Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection (DEFeND): a randomised external pilot trial

By

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ABSTRACT

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Background

Complications after major surgery are a significant cause of morbidity and mortality. Neck Dissection (ND) is one of the most commonly performed major operations in Head and Neck Surgery (HNS). Significant surgical complications occur in approximately 10 – 40% of all patients.

A systematic review and meta-analysis of randomised controlled trials (RCT) suggests that Fibrin Sealants (FS) may have potential clinical advantages in HNS through the reduction of complications, volume of wound drainage and retention time of the drains. So far, all RCTs have been single centre explanatory studies that lack external validity and are of variable quality. The paucity of high-quality pragmatic trials means that a surgical trial to determine the effectiveness of FS in reducing the rate and severity of complications in patients undergoing lateral neck dissection is warranted. The DEFeND randomised external pilot trial (REPT) will address critical questions on how well key components of the proposed study design work together as well as the feasibility of a definitive trial.

Currently a Core Outcome Set (COS) for HNS does not exist and there is a paucity of patient centred outcome measures specific to HNS. A scoping review of surgical COS is proposed to guide the direction of future HNS outcomes research.

Methods

The trial design that is being piloted is that of a two arm, parallel group, superiority trial with block randomisation in a 1:1 allocation ratio. The interventional arm will constitute the application of FS (ARTISS, Baxter Healthcare Ltd) to the surgical wound following completion of ND in addition to standard of care (SoC). The control arm will constitute SoC alone. Patients will be recruited from two sites, Aintree University

Hospital (AUH) and Queen Victoria Hospital (QVH). Eligible patients will include patients who require a lateral neck dissection with a minimum of three cervical nodal levels. Patients who require bilateral neck procedures or undergoing immediate reconstruction with free or regional flaps will be excluded. The outcomes being assessed are recruitment rate; screened to randomisation rate; fidelity of blinding process using blinding indices; number of missing or incomplete data entries; number of protocol deviations; number of losses to follow-up.

A scoping review of surgical COS registered with the COMET database will be undertaken. Only COS in which patients or their carers are stakeholders will be included. The suitability of outcome measures proposed for the definitive DEFeND trial will also be discussed.

Results

Overall, the trial recruited ahead of time and target. Out of 101 eligible patients 48 (47.5%) were randomised successfully at a rate of 5.3 patients per month. Five patients were withdrawn from the trial before surgery due to a change in treatment plan that meant they were no longer eligible. Blinding of patients, Research Nurses and outcome assessors was effective as determined by blinding indices. Missing outcome data was low and there were no differences between treatment arm and site. Two significant protocol deviations were reported relating to the allocation reveal at a specific time point during surgery. Both occurred early in the trial and were not repeated after corrective and preventative actions. Two (4%) patients were lost to follow-up.

The scoping review yielded 207 outcomes from 19 surgically relevant COS published between 2014 – 2020. Outcomes were classified (humanistic (71), complications (57), measurements (39), resource use (22), mortality (18)). Humanistic and complication outcomes were the most frequently utilised in surgical COS.

Conclusion

The DEFeND REPT has demonstrated that many components of the trial design work well together and a definitive pragmatic trial is feasible. Refinements in trial design and conduct are discussed and have the potential to improve the performance of the trial even further. The process has also revealed an important deficiency in patient centred outcomes that needs to be addressed before a definitive trial can be commenced. The validity and reliability of the Clavien-Dindo classification of surgical complications is discussed. Developing a COS for HNS trials is an important first step in identifying and developing patient centred

outcomes. Consideration should be given to using patient reported outcome measures (PROM) for subjective core outcomes. This study has shown that PROMs are both acceptable and feasible in HNS trials.

DECLARATION

I hereby certify that this dissertation constitutes my own product, that where the language of others is set forth, quotation marks so indicate, and that appropriate credit is given where I have used the language, ideas, expressions or writings of another.

I declare that the dissertation describes original work that has not previously been presented for the award of any other degree of any institution.

Signed,

Mandeep S. Bajwa

"This dissertation contains material that is confidential and/or commercially sensitive. It is included here on the understanding that this will not be revealed to any person not involved in the assessment process".

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GLOSSARY OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Events
aPTT	Activate Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AUC	Area Under the Curve
AUH	Aintree University Hospital
BAHNO	British Association of Head & Neck Oncologists
BBI	Bang Blinding Index
BMI	Body Mass Index
CA	Carotid Artery
Ca^{2+}	Calcium
CAPA	Corrective & Preventative Action
CC	Complexity & Comorbidity
CCI	Comprehensive Complication Index
CDC	Centre for Disease Control & Prevention
CE	Conformitè Europëenne
CI	Confidence Interval
CI	Chief Investigator
ClinROM	Clinician Reported Outcome Measure
CO_2	Carbon Dioxide
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COS	Core Outcome Set
CRN	Clinical Research Network

CRT	Chemoradiotherapy
CTIMP	Clinical Trial of an Investigational Medicinal Product
DASH	Disability of the Arm, Shoulder and Hand score
DGH	District General Hospital
DIC	Disseminated Intravascular Coagulation
DRF	Doctoral Research Fellowship
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
eLND	Elective Lymph Node Dissection
ENT	Ear, Nose & Throat
FDA	US Food & Drug Administration
FS	Fibrin Sealant
GA	General Anaesthesia
GCP	Good Clinical Practice
GI	Gastrointestinal
GP	General Practitioner
Hb	Haemoglobin
HDU	High Dependency Unit
HE	Health Economic
HNC	Head & Neck Cancer
HNS	Head & Neck Surgery
HPV	Human Papilloma Virus
hr	Hour
HRG	Health Resource Group
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IDEAL	Idea, Development, Exploration, Assessment, Long-term study
IDMSC	Independent Data Monitoring & Safety Committee
IJV	Internal Jugular Vein
ILND	Inguinal Lymph Node Dissection
IMP	Investigational Medicinal Product
IQR	Interquartile Range
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information Technology
ITT	Intention to treat
IU	International Unit
IU/mg	International Units per milligram
IU/ml	International Units per millilitre
JBI	James Blinding Index
KIU	Kallidinogenase Inactivator Unit
LCTU	Liverpool Cancer Trials Unit
LCTC	Liverpool Clinical Trials Centre
LoS	Length of Stay
LQ	Lower Quartile
LTD	Limited
MCID	Minimal Clinically Important Difference
MD	Mean Difference
MDT	Multidisciplinary Team
MeSH	Medical Subject Heading
Mg	Milligrams
ml	Millilitres

MM	Malignant Melanoma
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
ND	Neck Dissection
NDII	Neck Dissection Impairment Index
NEC	Not Elsewhere Classified
NHS	National Health Service
NIHR	National Institute of Health Research
NOAC	Novel Oral Anticoagulant
NWSTC	Northwest Surgical Trials Centre
ºC	Degrees Celsius
OMF	Oral and Maxillofacial
OPC	Oropharyngeal Carcinoma
OR	Odds Ratio
PDF	Portable Document Format
PE	Pulmonary Embolism
PET-CT	Positron Emission Tomography – Computer Tomography
PFS	Pilot and feasibility study
PI	Principle Investigator
PIC	Patient Identification Centre
PIS	Patient Information Sheet
PROM	Patient Reported Outcome Measure
PS	Performance Status
PT	Prothrombin Time
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QVH	Queen Victoria Hospital
RCT	Randomised Controlled Trial

REC	Research Ethics Committee
REPT	Randomised External Pilot Trial
RN	Research Nurse
ROC	Receiver Operating Characteristic
RR	Relative Risk
RT	Radiotherapy
SAE	Serious Adverse Events
SCM	Sternocleidomastoid Muscle
SEM	Standard Error of the Mean
SIV	Site Initiation Visit
SmPC	Summary of Product Characteristics
SN	Sentinel Node
SoC	Standard of Care
SPADI	Shoulder Pain and Disability Index
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SQRT	Square Root
SSI	Surgical Site Infection
SUSAR	Serious Unexpected Serious Adverse Reaction
TARDIS	Treatment Allocation Randomisation System
TC	Trial Co-ordinator
TIA	Transient Ischaemic Attack
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoL	University of Liverpool
UQ	Upper Quartile
UW-QoL	University of Washington – Quality
V	Variance estimate

VAS	Visual Analogue Scale
VATS	Video Assisted Thorascopic Surgery
VTE	Venous Thromboembolism
WHO	World Health Organisation
WHQ	Wound Healing Questionnaire
µmol	Micromole

Chapter 1. INTRODUCTION

1.1 Overview

This Introduction will cover key background information relating to the DEFeND randomised external pilot trial. A thorough explanation of what a Neck Dissection (ND) involves and the common complications that patient's experience will be provided. A complete discussion of the mechanism of action of Fibrin Sealants (FS) as well as a summary of existing evidence will also be discussed. Following on from this, the rationale for a randomized external pilot trial (REPT) prior to a definitive trial will be discussed.

1.2 Neck Dissection

Head and neck cancers (HNC) encompass a heterogeneous group of cancers that are collectively ranked the 8th most common cancer in the UK with approximately 12,000 new cases every year; this equates to 3% of all new cancer cases. In 1993 the incidence of HNC was 15 per 100,000 population and in 2017 the incidence increased to 20 per 100,000 population.(1)

The reason for this increase is likely to be multifactorial. Since the incidence of HNC increases with age, an ageing population is likely to be the most significant factor.(1, 2) HNC predominantly affects males, however the proportion of females is increasing. This may be explained by the fact that females have a longer life expectancy and therefore represent a greater proportion of cases in older age groups.(2) Oropharyngeal cancers (OPC) have seen the sharpest rise in incidence with a 100% increase between 2002 and 2011. In part, this is due to a rise in Human Papilloma Virus (HPV) induced tumours which are attributable to changes in sexual behaviour that have occurred over time. However, OPC has seen a proportionate rise in HPV negative cases too. Smoking and alcohol consumption are the main aetiological factors for

HPV negative cases. Interestingly adult smoking rates have declined in the UK however alcohol consumption has increased. This change in societal behaviour may explain why the oropharynx, which is exposed to alcohol during the act of swallowing, has seen a sharp rise in cases but the larynx which is protected from alcohol but exposed to smoking is more stable.(3)

The management of HNC may involve surgery, radiotherapy, chemotherapy or a combination of these treatments. The management of the neck forms a key part of the decision-making process when considering surgery. Metastatic spread to regional lymph nodes is one of the most important prognostic indicators in patients with HNC.(4) In patients with Squamous Cell Carcinoma (SCC), It has been reported that the presence of cervical lymph node metastases drops overall survival by 50%, this is even worse if there is evidence of extracapsular spread.(5, 6) The importance of regional lymph node metastases was recognised as early as 1905 when Crile first described the 'en-bloc' dissection of the neck.(7)

ND is a surgical procedure that involves removal of lymph nodes (lymphadenectomy) and surrounding tissues from within the neck. The reasons for performing a ND can be for staging and/or therapeutic purposes. In patients without clinical evidence of lymph node metastases ND may be performed to stage the neck and identify possible occult disease. The purpose of staging the neck is to enable decisions regarding adjuvant treatment such as Radiotherapy (RT) or concurrent Chemoradiotherapy (CRT) as well as providing prognostic information. In the presence of clinical and/or radiological lymph node metastases ND has a therapeutic role. ND can also be performed in the salvage setting if the patient has had primary RT/CRT. Figure 1 shows the various neck levels with their anatomical relationships. The levels demonstrated can be utilised for description of areas dissected during a lateral ND.

Historically, Neck Dissections (ND) were radical by today's standards and consequently carried high levels of morbidity without necessarily conferring a survival advantage. With advancements in surgery, anaesthesia and adjuvant treatments these operations are now selective and aim to preserve as much function as possible.(8) Currently, Neck dissection is the second most

commonly performed head and neck surgical procedure after resection of the primary tumor with approximately 2000 neck dissections being performed annually in England.(9)The rising incidence of HNC and the fact that ND is one of the most commonly performed major operations in HNS makes research into the improvement of patient outcomes following neck dissection a priority.

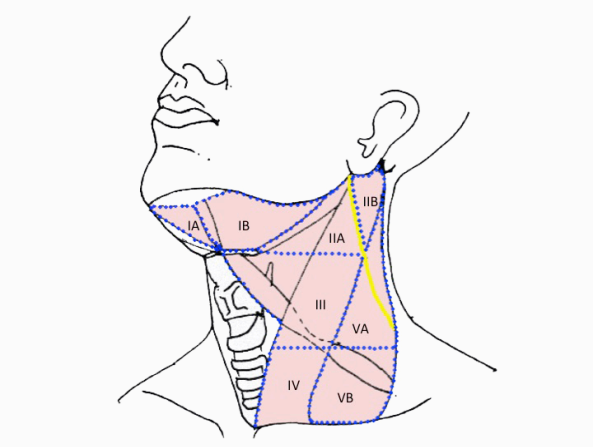


Figure 1 Neck levels

1.2.1 Overview of surgical technique and relevance to morbidity

The choice of incision is dependent upon surgeon preference, maximising access to the planned levels of dissection and the location of existing neck skin creases to hide the scar. In general, most incisions will start at the mastoid tip, travel down along the Sternocleidomastoid (SCM) muscle before curving anteriorly towards the midline. Figure 2 demonstrates three commonly used incisions that can be modified to access the lateral neck. The vascular supply of the cervical skin is derived from the external carotid artery superiorly and the subclavian artery inferiorly. Incisions which involve trifurcations (Figure 2 righthand image) or run parallel to carotid artery are best avoided in patients that have had previous radiotherapy as there is a risk that impaired perfusion of the skin can result in wound breakdown and exposure of the great vessels.(10)

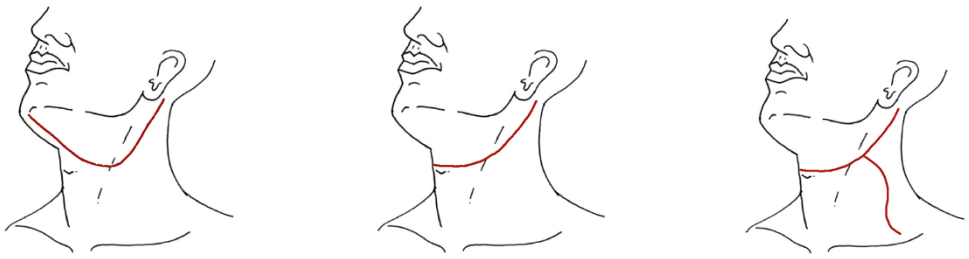


Figure 2 Commonly used neck incisions

After making the skin incision, skin flaps are raised in a subplatysmal plane to widely expose the anatomy to be dissected. The lymph nodes are contained within fibrofatty tissue that lies between layers of deep cervical fascia. Figure 3 shows this fibrofatty tissue being dissected off the underlying muscle while taking care to preserve neurovascular structures (if oncologically safe do so). Important structures include the contents of the carotid sheath (Internal Jugular Vein (IJV), Carotid Artery (CA), Vagus Nerve), Marginal Mandibular branch of Facial Nerve, Spinal Accessory Nerve, Hypoglossal Nerve, Phrenic Nerve and Thoracic Duct.

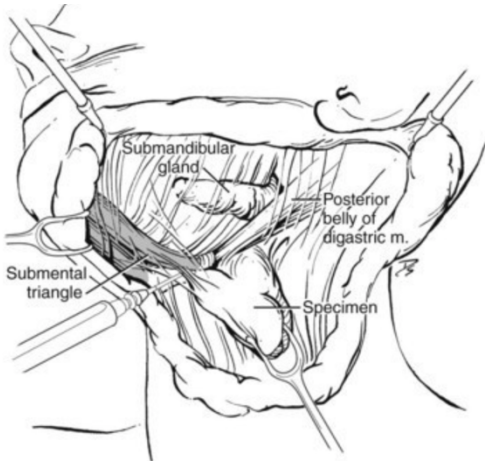


Figure 3 Tissue containing lymph nodes being dissected off underlying muscle in level IB. (Image taken from Atlas of Head & Neck Surgery(11))

Care must be taken when dissecting around these structures to ensure they are preserved. Iatrogenic injury to either the IJV or CA can result in profuse bleeding that needs to be addressed immediately. Because the CA is a substantial thick-walled vessel, vascular injury is

almost unheard of apart from cases where the vessel has been significantly damaged by previous irradiation, exposed due to wound breakdown or surgical site infection (SSI) or is closely associated with tumour. Iatrogenic injury to the IJV that requires repair is more common and reported to occur in 2.4% of neck dissections.(11) Once the surgeon has proximal and distal control of the vessel, repair is relatively straightforward. However, if injury occurs at the superior and inferior limits of the neck repair can be very difficult and will often result in significant blood loss. In addition to bleeding, IJV injury can result in an air embolus. Once Injury to the IJV has occurred it is important to apply pressure immediately, inform the anaesthetist and place the patient in the Trendelenburg (head down) position.(10) It is often necessary to ligate branches of the IJV and External CA. Care must be taken to ensure that the vessels are ligated securely to prevent post-operative bleeding.

The Thoracic Duct is a lymphatic structure that originates from the cisterna chyli at the level of the second lumbar vertebra. It ascends cranially to eventually reach the root of the left neck. Where it terminates into the venous circulation. It enters the IJV in 46% of cases, the confluence of the IJV with the Subclavian Vein in 32% and the Subclavian Vein in 18%.(12) Care must be taken when dissecting this area of the neck to avoid iatrogenic injury to the thoracic duct. Injury will result in a chyle leak which, if recognised intra-operatively, can be repaired. Often injury is not recognised until the patient commences diet post-operatively.

Neural injury can have a significant impact on the patient's post-operative recovery and long term quality of life. In the immediate post-operative period, injury to the Vagus Nerve can result in dysphagia and aspiration. If it occurs below the Nodose Ganglion it may result in Vocal Chord paralysis.(13) Injury to the Phrenic Nerve can cause paralysis of the hemidiaphragm and result in basal atelectasis of the lung and subsequent chest sepsis. Injury to the Hypoglossal Nerve can cause paralysis of the ipsilateral side of the Tongue. This can have a significant impact on the patients ability to swallow resulting in aspiration and feeding tube dependence.(10, 13)

Injury to the Spinal Accessory Nerve can cause shoulder dysfunction and pain. Injury to the Marginal Mandibular branch of the facial nerve can cause lower lip asymmetry and impaired function. Whilst these complications may not have a significant impact in the immediate post-operative period they are widely recognised to reduce the patients longer term quality of life.(14, 15)

An important part of the dissection involves removing the deep cervical chain of lymph nodes. These lymph nodes lie near the IJV. Figure 4 demonstrates the fibrofatty tissue containing these lymph nodes being dissected off the SCM and IJV. Once the neck dissection specimen has been removed the resulting wound has a large surface area with undermined skin flaps and muscle, exposed blood vessels and areas of surgical 'dead space'. Dead space can be defined as the space between the dissected structures where blood and fluid can collect. The collection of blood or other fluids within this space can result in complications e.g. haematoma or seroma formation which can result in delayed wound healing, SSI and may compromise the patient's airway.

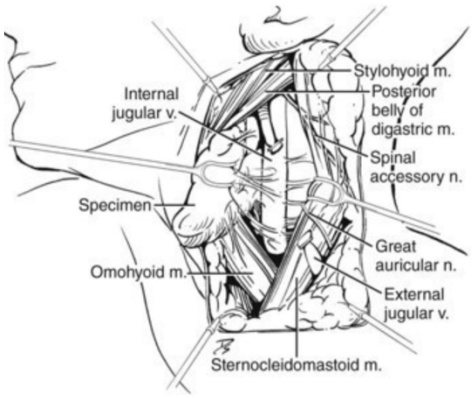


Figure 4 Demonstration of surgical dead space created by dissecting levels II and III off the Internal Jugular Vein. (Image taken from Atlas of Head & Neck Surgery(11))

1.2.2 Neck dissection complications

Complications after major surgery are a significant cause of morbidity and mortality in patients. As previously mentioned, ND is one of the most frequently performed major operations in the NHS and carries a complication rate of up to 30%.(16) Recently published qualitative research to develop a core information set for patients undergoing HNS demonstrated that “the likelihood of wound problems” and “details of major or common complications” were a priority for both patients and healthcare professionals during the consent process.(17)

Complications following surgery may be thought of as specific to the procedure and resulting wound (e.g. surgical site infection) or more generalised and related to the patient undergoing surgery in the broader context (e.g. venous thromboembolism due to reduced mobility). Impaired wound healing has a direct impact on procedure specific complications as well as an indirect impact on generalised/systemic complications. The risks of impaired wound healing can be classified into local and patient factors. (18) Local factors are those that directly influence the nature of the surgical wound, whereas patient factors are related to the health of an individual and their ability to heal.(18) Local factors that lead to impaired wound healing include problems with tissue oxygenation and perfusion, infection and foreign body reaction. For example, patients who have previously undergone RT to the neck may have impaired wound healing due to microvascular damage and local tissue hypoxia.(19) Patient factors that lead to impaired wound healing include problems such as immunosuppression, poor nutrition, smoking, alcohol, diabetes and obesity. It is important to mention that all types of complications and their associated risk factors tend to be interrelated at some level e.g. a patient with a surgical site infection may develop sepsis that can result in a myriad of downstream effects on other organ systems (e.g. type 2 myocardial infarction or acute renal failure).

The severity of complications may be classified according to the widely used Clavien-Dindo classification.(20, 21) The authors first described the classification in 1992 and later revised it in 2004.(22, 23) The rationale behind classification development was to allow a comparison in outcomes between different surgical procedures and institutions. The revised version was

validated in a cohort of 6336 patients undergoing elective general surgery in the author's institution.(23) Despite being validated in general surgical procedures, the classification is used across multiple surgical specialties.(24-26) The revised classification is presented in Table 1.

Table 1 Clavien-Dindo Classification of surgical complications.(24)

Grade of Complication	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological intervention. Acceptable therapeutic regimens are drugs such as antiemetics, analgesia, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside**.**
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade III-a	Intervention NOT under general anaesthesia
Grade III-b	Intervention under general anaesthesia
Grade IV	Life-threatening complication requiring HDU/ICU management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction
Grade V	Death

HDU High Dependency Unit, *ICU* Intensive Care Unit.

Given that an ageing population is one of the key reasons behind the rise in HNC incidence in the UK,(2) it is important to understand and identify which patients are at risk of complications following surgery. The prevalence of comorbidities, disability, geriatric syndromes and social issues makes treatment planning and the prevention of complications in this population more

challenging. Watt et al recently published a systematic review and meta-analysis on identifying older adults at risk of harm following elective surgery. The study found that the geriatric syndromes of frailty and cognitive impairment were associated with the development of postoperative complications whereas chronological age was not.(27) This may be because there is a great deal of diversity amongst patients of the same chronological age and the severity of these geriatric syndromes is a better marker of a patient's physiological reserve and their ability to avoid complications. This is supported by evidence from the HNC literature which has demonstrated that frailty is associated with increased complications, mortality, length of stay and readmission rates.(28, 29) The evolving demographic of HNC patients with a shift towards a population with a greater prevalence of geriatric syndromes means that research into strategies that prevent complications is a priority.

Several small retrospective case series on complications following ND have been published in the Italian, Brazilian and Indian literature.(13, 30, 31) It is questionable how relevant this data is to clinicians working within the NHS setting. In a series of 119 patients Pellini et al reported an overall complication rate of approximately 20%. Haematoma was the most frequent complication occurring in 12% of patients (5% were considered 'massive' and 7% 'small'). Wound dehiscence occurred in 6%, seroma in 1.6% and chyle leak in 0.8%. This study found that previous treatment to the neck including CRT, RT and previous surgery (especially radical ND or modified radical ND) were risk factors for major wound complications.(30)

In a series of 708 NDs Dedivitis et al reported only 0.14% patients suffered with a haematoma/haemorrhage, 0.28% patients developed a wound infection, 0.42% developed a chyle leak, 6% developed superficial dehiscence/epidermolysis and 1.6% developed a deep dehiscence.(13)

In a series of 82 patients Malgonde reported an overall complication rate of 20%. Seroma occurred in 3.65% of patients, wound dehiscence occurred in 2.43%, wound dehiscence with haematoma occurred in 1.21%, chyle leak occurred in 2.43%, surgical site infection occurred in 1.21% and fistula in 1.21%.(31) It is evident from these retrospective case series that the

rate and type of complications reported is highly variable, not least because there are inherent differences in the inclusion criteria dependent on the case mix at each institution.

Complication rates that are more relevant to the NHS setting may be gleaned from the supplementary data provided by two UK based multicentre surgical RCTs. The “nationwide randomized trial evaluating elective ND for early-stage oral cancer” (SEND study) included 250 randomised patients recruited from 25 UK hospitals.(32) This trial compared elective ND to a ‘watch and wait’ approach in patients with small oral cavity tumours, no clinically evident neck disease and no prior treatment. Therefore, it would be reasonable to expect complication rates in the elective ND arm to be on the lower end of the spectrum in this study. Wound problems specific to ND occurred in 4% of patients. Haemorrhage/haematoma occurred in 13.9% of patients however, this figure includes haemorrhage that occurred from resection of the index tumour.(32)

The PET-CT surveillance versus neck dissection in advanced head and neck cancer (PET-NECK) trial randomised 564 patients recruited from 37 UK hospitals.(16) This trial compared PET-CT surveillance to ND in patients who had received primary CRT with advanced N2 or N3 disease. Therefore, it would be reasonable to expect complication rates to be on the higher end of the spectrum in this study. In the planned ND arm, surgical complications occurred in 29% of patients. The neck haematoma rate was 1.4% and the seroma rate was 0.3%. Infection was reported in 16% of patients however this was not limited to SSI (i.e., chest infections were included). (16, 33)

Kerawala published a literature review on the prevention of complications after ND. The effects of ‘patient factors’ such as poor nutritional intake, smoking and alcohol can be minimized by preoperative optimisation strategies e.g., early placement of feeding tubes to improve nutrition, smoking cessation and alcohol detox. The effects of ‘local factors’ can be minimized by asepsis, prudent use of antibiotics, meticulous surgical technique and the use of surgical drains.(10)

1.3 Surgical Drains in Neck Dissection

ND results in a wound with exposed great vessels and a relatively large area of dead space in which fluid may collect. Collections of fluid such as inflammatory exudate (seroma) or blood (haematoma) may impair wound healing and increase the risk of SSI.(34) If significant haemorrhage occurs post-operatively there is the additional concern of airway compromise. Airway compromise may present as bleeding directly into the airway or an expanding haematoma that compresses the adjacent structures and potentially narrows the upper airway. For these reasons surgical drains are widely used in ND. Indeed, all respondents in surveys of the Canadian Society of Otolaryngology and American Head and Neck Society used drains in ND.(35, 36) However, there is good counterevidence that drains are detrimental in thyroid surgery. In a systematic review of RCTs comparing thyroid surgery with drains and without, Woods et al reported that drainless surgery did not significantly increase the rate of re-operation for haematoma or wound collections requiring intervention. However, surgery with drains increased the rate of SSI, pain and length of stay (LoS). Importantly, patients undergoing lateral ND were excluded from this review.(37) Whilst there is no evidence to support drainless (lateral) ND, the review by Woods et al does suggest that drains placed in the neck are a nidus for infection. From a patient perspective, there are anecdotal reports from patients in the Aintree Head & Neck Cancer Research Forum state that drains are uncomfortable and an impediment to mobilisation. In addition to promoting better wound healing, timely removal of drains may reduce LoS which connotes health economic benefits to healthcare providers. On this basis a strong argument can be made to reduce the retention time of drains in ND

Surgical drains can be classified as passive (e.g., Penrose or Corrugated drains) or active (e.g., high- or low-pressure suction drains). The previously cited surveys of North American surgeons suggest that the majority use active drains.(35, 36) A prospective study comparing active and passive drains in ND found that passive drains were associated with a significantly higher rate of wound dehiscence associated with discharge of fluid.(38) The author's attributed this

observation to a failure of passive drains to adhere skin flaps to the underlying wound and permit the collection of fluid.

The threshold for drain removal is based on a balance of risk between retaining drains long enough to prevent fluid collections and removing them before they instigate SSI. The threshold may be defined by volume, appearance of fluid (i.e., once the fluid becomes more serous/clear), time or a combination of these factors. The majority of surgeons in North America use volume as the main indicator for drain removal with 30ml in a 24-hour period being the most popular threshold.(35, 36) The threshold of 30ml/24hrs is also common amongst different surgical specialties working in different anatomical areas but there is a surprising lack of objective evidence supporting it.(39, 40) some authors have compared 30ml/24hrs to 50ml/24hrs and found that the higher threshold promotes earlier drain removal without a significant increase in complications.(41, 42) Tamplen et al conducted a small randomized study and found that a cut-off of 100ml/24hrs was safe.(43) Equally, some authors have found that measuring drain output more frequently facilitates the achievement of the criteria for earlier removal.(44)

In summary, surgeons generally favour active drains over passive drains because they encourage adherence of the wound surfaces through negative pressure, thereby preventing fluid collections. Timely removal of drains is considered beneficial because they are a nidus for infection and associated with potential health economic benefits.

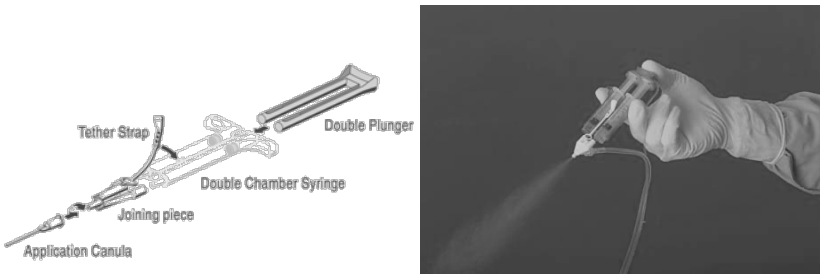
1.4 Fibrin Sealants

1.4.1 Introduction

FS are commercially available and US Food and Drug Administration (FDA) approved products that are derived from human blood and mimic the final stages of the coagulation pathway.(45) They have been extensively investigated in recent years, within several areas of surgery, as adjuncts to haemostasis.(46) The two key components of FS are Fibrinogen and Thrombin

which are mixed together and applied to the raw surfaces of the surgical wound prior to closure. Thrombin cleaves fibrinogen to form a fibrin clot that may seal small bleeding vessels. If the FS is applied more widely to the surgical field, it can also adhere the raw wound surfaces together thereby reducing surgical dead space. The ability to seal small vessels and reduce dead space has the potential to expedite healing after surgery, reduce complications and facilitate earlier drain removal. (47)

Baxter Healthcare LTD is a major global supplier of FS and along with Johnson & Johnson Services, Inc holds the majority market share, with Baxter leading in terms of revenue.(48) FS produced by these companies are commonly packaged as double chamber syringes, one chamber containing Thrombin and the other Fibrinogen as shown in Figure 5.(49, 50) The two active ingredients are mixed in the joining piece located at the tip of the syringe when the double plunger is depressed. There are several ways to apply FS to a wound surface including droplets via a cannula if targeting a small area (Figure 5A), or a spray driven by pressurised medical grade air or carbon dioxide (Figure 5B) if wide wound coverage is required.(51) As ND produces a wound with a relatively large surface area, the sprayable form is most relevant to this body of work.



A B

Figure 5 A: components of a fibrin sealant syringe and cannula for targeted application. B: fibrin sealant syringe being driven by medical grade air to produce a fine spray for wide wound coverage. (images taken from https://globaladvancedsurgery.baxter.com

1.4.2 History and licensing

The first use of Fibrin to promote wound healing was reported by Bergel in 1909.(52) However, the combination of thrombin with fibrinogen to produce a FS was first reported by Cronkite in the Journal of the American Medical Association in 1944 where it was described as a material that could adhere skin grafts to the wounds of soldiers with burns.(53) Due to low fibrinogen concentrations, the resulting FS was considered to have low adhesive strength. Also, at that time many patients became infected with viral hepatitis that was transmitted through the human fibrinogen. Due to the limited efficacy and the risk of transmitted infection the wound healing benefits did not outweigh the risk and further development of FS was halted in the US.(54) In the 1970s the introduction of industrial plasma fractionation methods allowed the production of more concentrated fibrinogen which improved the rheological properties of FS.(54)

The first commercially available FS that was made from human fibrinogen and thrombin was available in Europe in 1972.(55) In 1972 a German group described the successful application of FS to repair the nerves of rabbits.(56) They subsequently published their experience of using FS in human subjects in 1973.(57) However, due to the history of transmitted infections, FDA approval was delayed until 1998.(54) This approval was granted on the basis of a growing body of evidence supporting efficacy and safety as well as improved techniques for virus inactivation such as nanofiltration and heat pasteurization.(54) Tisseel (Baxter Healthcare LTD) was the first FS to be approved by the FDA.(58)

Following an updated guidance by the MHRA in 2014 there are currently four sprayable FS that are authorised in the UK: Evicel (Johnson & Johnson Inc), Tisseel (‘Lyo’ and ‘Ready to use’ have identical composition) and ARTISS (Baxter Healthcare LTD).(59) Table 2 describes their ‘on-label’ indications taken from their respective Summary of Product Characteristics (SmPC) documentation.(60-62)

Table 2 'On-label' indications for sprayable FS available in the UK (contents of table taken verbatim from respective Summaries of Product Characteristics).

Sprayable Fibrin Sealant	'On-Label' Indication for Use
Evicel(60)	Supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis Also indicated as suture support for haemostasis in vascular surgery and for suture line sealing in dura mater closure.
Tisseel (Lyo/Ready to use)(61)	Supportive treatment where standard surgical techniques are insufficient • For improvement of haemostatsis • As a tissue glue to promote adhesion/sealing, or as suture support: o In gastrointestinal anastomoses o In neurosurgery where contact with cerebro-spinal fluid or dura mater may occur • For mesh fixation in hernia repair, as an alternative or adjunct to sutures or staples.
ARTISS (62)	Adhere/seal subcutaneous tissue in plastic, reconstructive and burns surgery, as a replacement or an adjunct to sutures or staples. In addition, ARTISS is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces

1.4.3 Mechanism of action

Following surgical injury that results in bleeding, the body attempts to achieve haemostasis through the coagulation pathway (Figure 6). Primary haemostasis is the aggregation of platelets forming a plug at the site of blood vessel injury. Secondary haemostasis is achieved through the intrinsic and extrinsic pathways which converge to form the common pathway which activates fibrinogen into fibrin. The resulting fibrin strands cross-link to form a mesh which stabilises the platelet plug, forming a clot that attempts to seal the injured blood vessel. (55)

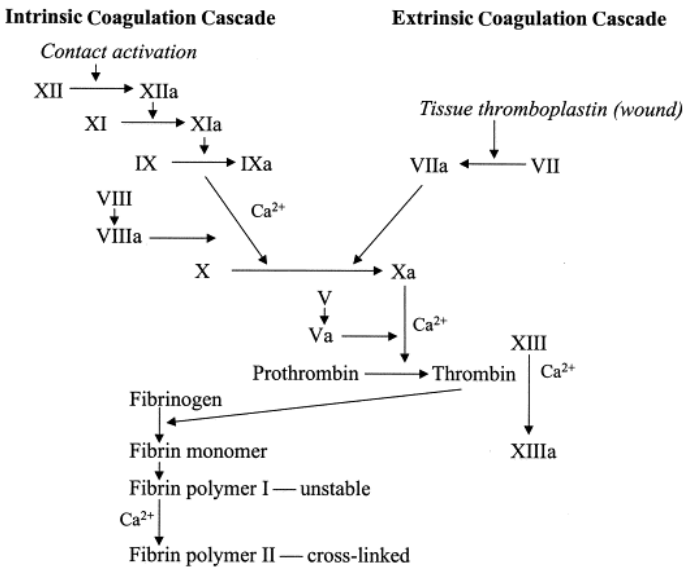


Figure 6 Coagulation pathway

FS mimics the final stages of physiological coagulation. Fibrinogen is split into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate to form the FS polymer or clot which is initially unstable (refer to Figure 6 Coagulation pathway). In the presence of calcium ions, thrombin catalyses the generation of Factor XIIIa from Factor XIII. Factor XIIIa has the effect of stabilising the FS polymer by cross-linking the fibrin fibres.(60-62)

The fibrin and thrombin components of FS can be manipulated depending on the desired haemostatic or adhesive effect. The adhesive strength of FS can be increased by increasing the fibrinogen concentration. Increasing the thrombin concentration increases the rate of polymerisation. If the desired effect is immediate haemostasis, a high thrombin concentration FS is desirable. If the desired effect is adhesion of skin flaps lower thrombin concentration allows necessary time for manipulation and positioning of tissues.(63)

Fibrinolytic activity induced by plasmin, a naturally occurring fibrinolytic enzyme, is increased as wound healing progresses. Aprotinin is an antifibrinolytic agent that prevents premature proteolytic degradation of the FS polymer. Ultimately FS is metabolised by the processes of fibrinolysis and phagocytosis in the same way as endogenous fibrin.(61)

A description of the key constituents of each of the sprayable FS authorised for use in the UK is provided in Table 3. The concentration of Fibrinogen is similar across all products but the Thrombin concentration varies. Evicel contains the highest concentration of thrombin but does not contain an antifibrinolytic agent, therefore polymerisation will occur quickly but the FS polymer will also be metabolised quickly. Tisseel contains a high concentration of thrombin, therefore polymerisation will occur quickly and the presence of Aprotinin will inhibit early degradation of the FS polymer. ARTISS contains a low concentration of thrombin, therefore polymerisation will take longer and the presence of Aprotinin will inhibit early degradation of the FS polymer. These concentrations suggest that Evicel and Tisseel are primarily haemostatic agents and ARTISS is primarily an adhesive agent.(60-62)

Table 3 Key constituents of sprayable fibrin sealants. *Concentration of Calcium Chloride not provided in Summary of Product Characteristics. **Kallidinogenase Inactivator Unit.

Fibrin Sealant	Sealer Protein Solution	Thrombin Solution
Evicel(60)	55 – 85 mg/ml Human Fibrinogen	800 – 1,200 IU Human Thrombin

		Calcium Chloride*
Tisseel(61)	91mg/ml Human Fibrinogen 3000 KIU**/ml Aprotinin	500 IU/ml Human Thrombin 40 µmol/ml Calcium Chloride Dihydrate
ARTISS (62)	91mg/ml Human Fibrinogen 3000 KIU**/ml Aprotinin	4 IU/ml Human Thrombin 40 µmol/ml Calcium Chloride Dihydrate

1.4.4 Role of Fibrin Sealants in patients with bleeding disorders

Up to this point, FS has been considered as an adjunct to haemostasis and wound healing in patients that have normal physiology. It is also important to understand the role of FS when these processes have been disrupted by disease or medication. Patients who have a tendency to bleed pose a challenge to surgeons across all specialties necessitating involvement of Haematologists and perioperative optimisation. Table 4 describes some of the more common bleeding disorders encountered within surgical practice according to whether the condition is inherited or acquired.(64)

Table 4 Description of common bleeding disorders.(62)

Bleeding Disorder		Description
Inherited Bleeding Disorders	Haemophilia A	Inherited disorder due to deficiency in factor VIII
	Haemophilia B	Inherited disorder due to deficiency of factor IX
	von Willebrand's disease	Most common inherited bleeding disorder. Deffiiciency in von Willebrand factor resulting in a failure of platelet adhesion and deficiency in factor VIII

Acquired Bleeding Disorders	Thrombocytopenia	Low platelet count due to reduced production (leukaemia) or reduced life span (Idiopathic Thrombocytopenic Purpura)
	Anticoagulant treatment	Warfarin is a vitamin K antagonist which predominantly affects the extrinsic pathway. It inhibits the production of dependent clotting factors Thrombin, VII, IX, X.(65) Heparin binds to and increases activity of Antithrombin III which in turn inactivates several factors, but most importantly Thrombin and factor X. It predominantly affects the intrinsic pathway.(65) Novel Oral Anticoagulants (NOAC) work by directly inactivating either Thrombin (e.g. Dabigatran) or factor Xa (e.g. Rivaroxaban, Apixaban, Edoxaban).(65)
	Liver Disease	Liver produces most clotting factors. Patients with liver failure may also have thrombocytopenia.
	Disseminated Intravascular Coagulation	Complication of an underlying disorder that causes widespread endothelial damage. This results in systemic activation of the clotting cascade and rapid depletion of factors and platelets

Effective use of FS has been reported by Martinowitz et al in patients with haemophilia A, B and von Willebrand's disease undergoing oral surgery, trauma and orthopaedic surgery and urology. The use of FS in these patients was reported to lead to a reduction in perioperative bleeding and coagulation factor supplementation.(66)

Milic et al reported that FS reduced the number of haematomas in patients who were anticoagulated with either heparin or warfarin after pacemaker insertion.(67) This evidence is supported by Bodner et al who reported FS reduced bleeding after oral surgery in anticoagulated patients.(68) There are currently no studies that report on the effectiveness of FS in patients on NOAC treatment or who suffer from thrombocytopenia.

No detailed explanation of how and why FS is effective in patients with bleeding disorders has been provided by the authors of these articles. As Table 4 demonstrates, most conditions (apart from DIC) are associated with deficiencies of clotting factors upstream of the conversion of fibrinogen to fibrin in the coagulation pathway. One may cautiously postulate that FS provides an exogenous source of fibrinogen and thrombin that is sufficient to overcome the patient's deficiency and facilitate haemostasis.

Referring back to section 1.4.3, FS requires endogenous factor XIII to stabilize the final fibrin polymer. According to the SmPC of the sprayable FS products, none contain exogenous factor XIII. (60-62) No studies assessing the effectiveness of FS in patients with factor XIII deficiency (a very rare condition that affects 1 in 1 – 3 million people worldwide(69)) have been performed at the time of writing. Again, one may cautiously postulate that FS without additional exogenous factor XIII may have impaired effectiveness in these patients. Dickneite et al have reported improved rheological properties of FS when factor XIII is added in an animal model.(70) Beriplast P produced by CSL Behring, Germany is a commercially available FS which contains factor XIII, however, it is not licensed for spray application in the UK.(71)

1.5 Evidence for Fibrin Sealants in Surgical Literature

Edwards et al conducted an extensive and detailed systematic review of Randomised Controlled Trials (RCTs) and observational studies on the use of FS across all non-emergency surgery.(46) The primary outcome measures of interest were prevention of seroma and haematoma development. Across all surgical specialties the meta-analysis did not identify a significant benefit for FS over standard of care (SoC) in the prevention of seroma (OR 0.84, 95% CI 0.68 to 1.04; p = 0.13; I^2 = 12.7%). However, there was a statistically significant effect for FS compared with SoC in the prevention of haematoma (OR 0.62, 95% CI 0.44 to 0.86; p = 0.01; I^2 = 0%). This was primarily driven by the results for hernia surgery (OR 0.22 95% CI 0.06 to 0.74; p = 0.01; I^2 = 0%). There was a trend for haematoma prevention in the other surgical specialties, but it was not statistically significant. A post hoc analysis that combined both seroma and haematoma prevention showed a statistically significant benefit for FS versus SoC (OR 0.77, 95% CI 0.64 to 0.92; p = 0.01; I^2 = 6.7%).(46)

Regarding secondary outcomes, there was no statistically significant difference between FS and SoC in the prevention of post-operative haemorrhage (OR 0.64, 95% CI 0.40 to 1.02; p = 0.08; I^2 = 0%) or the prevention of SSI (OR 0.76, 95% CI 0.54 to 1.06; p = 0.12; I^2 = 0%). However, FS did significantly reduce the rate of reoperation (OR 0.65, 95% CI 0.48 to 0.87; p = 0.00; I^2 = 0%). Fibrin sealants were also shown to reduce the length of hospital stay for people undergoing Upper GI, Cardiothoracic and Breast surgery. The duration of post-operative drainage was also slightly reduced by FS for Breast surgery (fixed-effects model: MD –0.50 days, 95% CI –0.68 to –0.33 days; p < 0.01; I^2 = 90.6%; random-effects model: MD –1.06 days, 95% CI –1.69 to –0.42 days; p = 0.01) and Cardiothoracic surgery (fixed-effects model: MD –0.46 days, 95% CI –0.53 to –0.39 days; p < 0.01; I^2 = 91.0%; random-effects model: MD –2.10 days, 95% CI –3.65 to –0.56 days; p = 0.01).(46)

Interestingly Edwards et al provide the results of their meta-analysis using both fixed- and random-effects models.(46) Under the fixed-effect model we assume that the “true” effect size for

all studies is the same and the observed differences are due to sampling error. Under this model, greater weight is given to larger studies as they provide better information about the "true" effect size. Whereas the random-effects model estimates the mean of the different effect sizes. Under this model, all effect sizes are represented and not given less weight because they are from smaller studies i.e. the overall estimate is not inordinately influenced by any single study. The fixed-effect model is advisable if two conditions are met: firstly, all included studies are clinically and methodologically homogeneous; secondly, the aim is to calculate the common effect size for a specific population and not to generalise to other populations. However, when accumulating data from studies that have been performed by different researchers operating independently, it is unlikely that the studies will be homogeneous. There is a likelihood that any one of several elements (e.g. the patient sample, the nature of the intervention or the method of intervention delivery) might be different, therefore, a common "true" effect size cannot be assumed. Furthermore, if the aim of the analysis is to generalise the results beyond the included studies, as is the case with Edwards et al, a random-effects model is more appropriate. A caveat to using random-effects models is that they should only be employed when analysing a large number of studies (e.g. >5) On this basis, meta-analyses of FS trials across different surgical specialties, institutions and patient samples should use the random-effects model.(72)

In summary, whilst the review by Edwards et al is extensive and detailed, it includes a very broad range of surgical procedures performed for different conditions within the same analyses. The results of this systematic review suggest that the efficacy of FS may vary across different surgical procedures and anatomical sites.(46) In order to understand the role of FS in ND it is important to review more specific evidence. However, prior to this body of work no systematic review on the role of FS in ND had been performed. Therefore, it is relevant to review the evidence of FS in other lymphadenectomy procedures that may have, at least a degree of applicability to lymphadenectomy in the neck.

1.5.1 Evidence for Fibrin Sealants in lymphadenectomy procedures

Lymphadenectomy procedures are commonly performed in the neck, the axilla or the groin. Despite being in different anatomical locations the procedures share some similarities. These similarities include: the removal of lymphatic tissue around important neurovascular structures; The creation of dead space that often requires a surgical drain; they are performed as part of the management of malignant disease that drains into that specific lymph node basin. It is therefore interesting to note that the morbidity of these procedures is very different. This may be related to the different types of malignancy being treated and the demographic/risk profile of patients. However, the difference between procedures still exists in patients being treated for malignant melanoma (MM). Depending on the site of the index tumour, MM can drain to the neck, axilla or groin. This may necessitate lymphadenectomy in any of the three sites while sharing a broadly similar pathology and patient population. In a review of 236 consecutive lymphadenectomy procedures for MM, Akkooi et al reported much higher rates of wound infection and seroma in inguinal lymph node dissection (ILND) compared to axillary or neck dissection.(73) Furthermore, seroma formation was more common after axillary dissection compared to the neck. Rates of postoperative bleeding and nerve injury were similar across all sites. This suggests that the surgical site itself may influence the incidence and type of complications patients encounter.(73) The aetiology for these occurrences are not well documented but the following factors may have a role: the ability to obtain dependent drainage being easier in the neck and axilla; the ability to mobilise early being easier after neck and axillary surgery; the ability to establish collateral drainage of lymph being easier in the neck than in the limbs; the patient's ability to maintain a clean and dry surgical site. Given these proposed differences, one may infer that the efficacy of FS may also be different according to the surgical site.

Weldrick et al conducted a systematic review of RCTs on the use of FS in ILND.(74) Only six studies met the eligibility criteria. All studies were reported to have some risk of bias (RoB) but often there was not enough detail to make an accurate RoB assessment. The meta-analysis was performed using a random effects model and no statistical heterogeneity between studies

was reported. Overall, FS did not have a positive impact on any of the outcomes assessed when compared to an unexposed control arm. The results of the meta-analysis are summarised. FS did not prevent wound Infection (RR 0.94 95% CI 0.68 – 1.32; p = 0.74); seroma (RR 1.00 95% CI 0.65 – 1.55; p = 0.99); seroma requiring drainage (RR 0.79 95% CI 0.42 – 1.47; p = 0.45); wound necrosis (RR 0.96 95% CI 0.27 – 3.47; p = 0.95); wound dehiscence (RR 1.09 95% CI 0.59 – 2.04; p = 0.78); haematoma (RR 0.71 95% CI 0.12 – 4.14; p = 0.70). There was a tendency towards FS reducing the number of drainage days, but this difference was not statistically significant (Weighted Mean Difference -2.64 days 95% CI -6.18 – 0.90; p = 0.14). Overall complications were reported in 2/6 trials. At least one post-op complication was seen in 55/88 (62.5%) patients in the FS arm and 57/89 (64%) in the unexposed control arm (RR 0.97 95% CI 0.77 – 1.21; p = 0.75).(74) Although this systematic review did not identify any significant benefit of FS, it is important to remember that the number of included studies was small. Therefore, it is difficult to make generalisations about the use of FS in ILND beyond the included studies and no firm conclusions can be made.

Sajid et al conducted a Cochrane Review on the role of FS in breast and axillary surgery.(75) 18 studies met the eligibility criteria. The authors concluded that the overall quality of evidence was inadequate and biased. When considering mastectomy alone OR combined mastectomy and axillary surgery, FS failed to reduce the incidence of seroma, mean volume of seroma, SSI, post-operative complications or length of stay. However, when only the trials that assessed the role of FS in combined mastectomy and axillary surgery were analysed (using the random-effects model) the results were marginally better. FS did not improve the incidence of seroma, mean volume of seroma, SSI or post-operative complications. However, it did influence total volume of drained seroma (Standardised Mean Difference -0.54 95% CI -1.06 – -0.02; p = 0.04; I^2 = 75.78%); number of drainage days (Standardised Mean Difference -0.68 95% CI -0.98 – -0.39; p <0.0001; I^2 = 85.77%); length of stay (Standardised Mean Difference -0.93 95% CI -1.23 – -0.62; p <0.0001; I^2 = 39.51%).(75)

There are several points to note when interpreting the review by Sajid et al.(75) Firstly, due to the methodological and statistical heterogeneity between studies the random-effects model was appropriately used. However, the sub-group analysis of mastectomy and axillary surgery trials needs to be interpreted with caution due to the small number of trials (7 in total) and the potential impact on the utility of the applied random-effects model.(75) Secondly, the use of Standardised Mean Difference rather than Weighted or Raw Mean Difference makes interpretation of the results more complex. Standardised Mean difference is a summary statistic used in meta-analysis when the studies assess the same outcome but do so in different ways (e.g. using different scales). This often makes interpretation of the intervention difficult because it is reported in units of standard deviation rather than in units of a scale.(76) It is therefore difficult to know whether the differences observed in the sub-group analyses discussed are clinically meaningful. Nevertheless, as with the review by Weldrick et al(74), the quality of evidence is poor and making firm conclusions about the role of FS in ILND and breast and axillary surgery is problematic.

An important but unreported observation in the Sajid review pertains to the types of FS used in the included studies. Tisseel was used as the interventional product in 6 studies, Tissucol in 5, Quixil in 1, Hemaseel in 1, Greemplast in 1, Autologous FS in 1 and the type of FS was unreported in 3.(75) The vast majority of these are high Thrombin concentration products(49, 63, 77) and therefore primarily designed for haemostasis rather than adhesion. The Thrombin concentration is unknown for 5 of these studies including Greemplast and Autologous FS making the generalisability of these particular studies extremely limited.

Benevento et al published an RCT on the role of the low thrombin concentration FS, ARTISS in axillary surgery.(78) This trial was published in 2014, after the review by Sajid et al. Although a small single-centre study with only 60 patients recruited, the results demonstrated a significant (both clinically and statistically) benefit of using ARTISS. The authors reported significantly less drainage volume, drainage time and length of stay.(78) Of course, the outcome of this isolated trial is not generalisable or conclusive but it does support the premise that low

Thrombin concentration FS may deliver clinically significant benefit where high Thrombin concentration FS has not. Lymphadenectomy procedures are routinely performed as 'open' surgical procedures where the surgeon has direct access to the wound. Sound surgical technique entails achieving good haemostasis via ligatures, clips or diathermy prior to wound closure. There should be minimal need to rely on FS for haemostasis however, due to the surgical dead space, there are potential benefits from adhesion. A low Thrombin concentration FS allows time for the surgeon to reposition the skin flaps and commence wound closure before the completion of polymerization.(51) The identifiable products included in the review by Sajid et al take a matter of seconds to commence polymerization (before tissue approximation would be completed), therefore limiting their efficacy as adhesive agents.(61, 75)

ARTISS has been approved for use in the UK and USA since 2009 and is the only FS marketed as having a low thrombin concentration for the purposes of adhesion (see section 1.4.3).(51) Very few RCTs have been conducted utilising ARTISS however results are largely encouraging. In a "split-face"single-centre RCT (where one side of the patient's face received the intervention and the other did not), Hester et al reported significantly reduced drainage volume after rhytidectomy on the side of the face that received Artis.(79) Pilone et al conducted a small single-centre RCT in post-bariatric patients undergoing abdominoplasty and found that ARTISS significantly reduced length of stay, seroma formation and complications.(80) In a multi-centre phase III RCT of patients with burns, Foster et al reported that using ARTISS to adhere skin grafts resulted in fewer seromas and haematomas.(81)

In summary, evidence gleaned from systematic reviews of RCTs suggests that FS does not provide significant benefit in patients undergoing lymphadenectomy procedures.(74, 75) However, the quality of trials as well as the statistical and methodological heterogeneity are issues that make any conclusions difficult. Furthermore, the type of FS used in the included trials are primarily haemostatic products. In the few trials that have used low thrombin concentration FS for adhesion, results have been encouraging but by no means conclusive.(78-81) Based on the findings of studies like Akkooi et al, it is clear that the different lymphadenectomy

procedures have a different complication profile.(73) Therefore to further understand the role of FS in HNS specifically, a systematic review on the subject was conducted.

Chapter 2. PRE-TRIAL SYSTEMATIC REVIEW OF FIBRIN SEALANTS IN HEAD AND NECK SURGERY

The conduct and outcomes of this systematic review were published prior to the doctoral research period.(82) However, the results and implications are of critical relevance to the justification and design of the DEFeND trial, justifying their inclusion.

2.1 Introduction

There have been three previously published systematic reviews on the use of tissue adhesives (not necessarily FS) in soft-tissue surgery of the head and neck region looking specifically at rhytidectomy and tonsillectomy.(83-85) The most recent systematic review on the use of tissue adhesives in rhytidectomy by Killion et al showed that their application significantly reduced the rate of haematoma formation and reduced the volume of surgical drainage. Sproat et al(85) published their systematic review on the use of tissue adhesives in tonsillectomy wounds in 2016 and found that they did not significantly reduce the rate of post-operative pain or bleeding. The authors commented on the fact that most studies were of low quality and were underpowered to detect statistical significance even when pooled in the meta-analysis.(85)

Prior to this work there have been no systematic reviews on the use of FS that encompass the entirety of soft-tissue head and neck surgery or even look specifically at thyroid surgery, parotid surgery or neck dissection. With a comprehensive understanding of the available evidence, decisions regarding the necessity of further research in this field can be made. To this end a systematic review of RCTs was conducted to answer the following questions regarding the application of FS in patients undergoing soft-tissue surgery of the head and neck region that would commonly require a surgical drain compared to a non-exposed control group:

1) Is there evidence that FS reduces the volume of wound drainage?

Is there evidence that FS reduces the time of surgical drain retention?

2) Is there evidence that FS reduces the time to discharge or time to being declared surgically fit for discharge?
3) Is there evidence that FS reduces the rate of clinically significant adverse events (AEs) defined as Clavien-Dindo(23) grade II or worse, or the rate of haematoma/seroma formation?
4) Is there evidence that FS reduces post-operative pain?
5) Is there evidence that FS allows a quicker return to normal function as documented by patient reported outcome measures?
6) Is FS considered to be an acceptable intervention by patients?
7) Is FS a cost-effective intervention?

2.2 Methods

A review protocol was established and prospectively registered on the 'PROSPERO: International Prospective Register of Systematic Reviews' website.(86) This study was written in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines.(87)

All published RCTs comparing FS to non-exposed controls, published during any year and written in any language including adult patients of any gender or ethnicity having soft-tissue surgery of the head and neck anatomical region that would commonly require the placement of a surgical drain were included. RCTs that included patients having FS applied to bone, cartilage, dental, ocular, middle ear or intra-cranial tissues were excluded except if the FS was used to close the soft tissue dead space created to access underlying structures.

The following databases were searched: EMBASE (1974 to July 2016); MEDLINE (1946 to October 2016); PubMed (start of records to November 2016); Cochrane Library and Central

Register of Controlled Trials (October 2016); ClinicalTrials.gov (October 2016); World Health Organisation International Clinical Trials Registry Platform (October 2016). The website "Research Gate" was also searched for unpublished work, conference presentations or posters (October 2016). The search strategy using MeSH terms was as follows: ("head and neck neoplasms" or "otorhinolaryngologic diseases" or "otorhinolaryngologic surgical procedures" or "oral surgical procedures" or "dermatologic surgical procedures" or "cervicoplasty" or "rhinoplasty" or "lymph node excision" or "salivary gland" or "stomatognathic diseases" or "craniocerebral trauma" or "neck injuries") and ("controlled clinical trials" or "systematic review" or "meta-analysis" or "randomised controlled trial as topic") and ("fibrin tissue adhesive"). The search was limited to humans.

The study selection process was carried out by uploading the search results from all databases to "EPPI-Reviewer 4: software for systematic reviews" (Social Science Research Unit, University of London). This software also facilitated the removal of duplicate studies. Two reviewers (Bajwa; PhD candidate and Schache; primary supervisor) selected studies by screening the title and abstract and then repeating the process using full-text versions of studies that cleared the first stage of screening. Studies were excluded if it transpired that they were based on excluded surgical procedures (as previously mentioned), did not specifically use FS or were not the correct study design. All resultant studies that cleared the second round of screening were included in the systematic review and meta-analysis. There were no conflicts of opinion between the two authors applying the inclusion and exclusion criteria.

Data was collected in keeping with the guidance published in the "Cochrane Handbook for Systematic Reviews of Interventions" version 5.1.0. The quality assessment was carried out using the Cochrane Collaboration's tool for assessing risk of bias which can be found in the handbook.(88) This was also performed independently by two reviewers assessing: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of

bias. Each source of bias was reported as low risk, uncertain or high risk. Clearly blinding of the surgeon poses challenges in the study design so in terms of performance bias, un-blinding the surgeon at the point of wound closure was the minimum acceptable standard.

The primary outcomes of interest in this review were 'volume of drainage' and 'time of drain retention.' Secondary outcomes were 'time to hospital discharge' or 'being declared surgically fit for discharge,' 'wound complications or adverse events,' 'post-operative pain,' 'time to return to normal function using patient reported outcome measures,' 'patient acceptability to FS' and 'cost analysis.' Data was collected using a spreadsheet with predetermined column headings for each data entry and was trialled on the first two studies. Where important information was lacking formal requests were made to the corresponding authors. In order to standardise the severity of complications the Clavien-Dindo classification was used.(23) Only complications of grade II (see Table 1) or worse were considered significant.

2.2.1 Statistical analysis

Data was analysed using RevMan version 5.3.5 software (Cochrane Collaboration). For each trial the difference in means and 95% confidence interval were calculated for continuous outcomes and the risk ratio and 95% confidence interval calculated for dichotomous outcomes. Individual trial effects were combined using a random effects inverse variance weighted method for continuous outcomes and Mantel-Haenszel method for dichotomous outcomes. The degree of heterogeneity was assessed using the I^2 statistic and sensitivity analyses assuming a fixed treatment effect undertaken for comparison. If authors chose to present their continuous data as median and interquartile range (IQR) then it was assumed the data was skewed. The authors were approached for the actual mean and standard deviation (SD). If there was no response and the degree of skewness was minimal then it was considered appropriate to estimate the mean and SD for the purposes of meta-analysis, accepting the limitations of this approach.(89) The mean and SD was also estimated if the authors did not respond and presented their data as median with minimum and maximum values.(90) If adequate

data permitted, the following subgroup analyses had been planned to compare the surgical procedure performed (e.g. thyroidectomy); the type and volume of fibrin adhesive used; use of harmonic scalpel or similar thermo-coagulation device for haemostasis; type of post-operative drainage (e.g. active versus passive, open versus closed); the maximum volume of drain output over 24 hours that was considered safe to remove the drain.

2.3 Results

A total of 421 articles were identified after duplicates were removed from the various searches. Of these 11 studies were included in the final review and meta-analysis. A total of 522 patients were randomised across these 11 studies, including 180 patients in rhytidectomy trials that were 'split-patient' controlled trials (i.e. rhytidectomies were bilateral procedures and patients were randomised according to whether the right or left side received FS). Figure 7 provides details of the screening processes in the form of a PRISMA diagram.

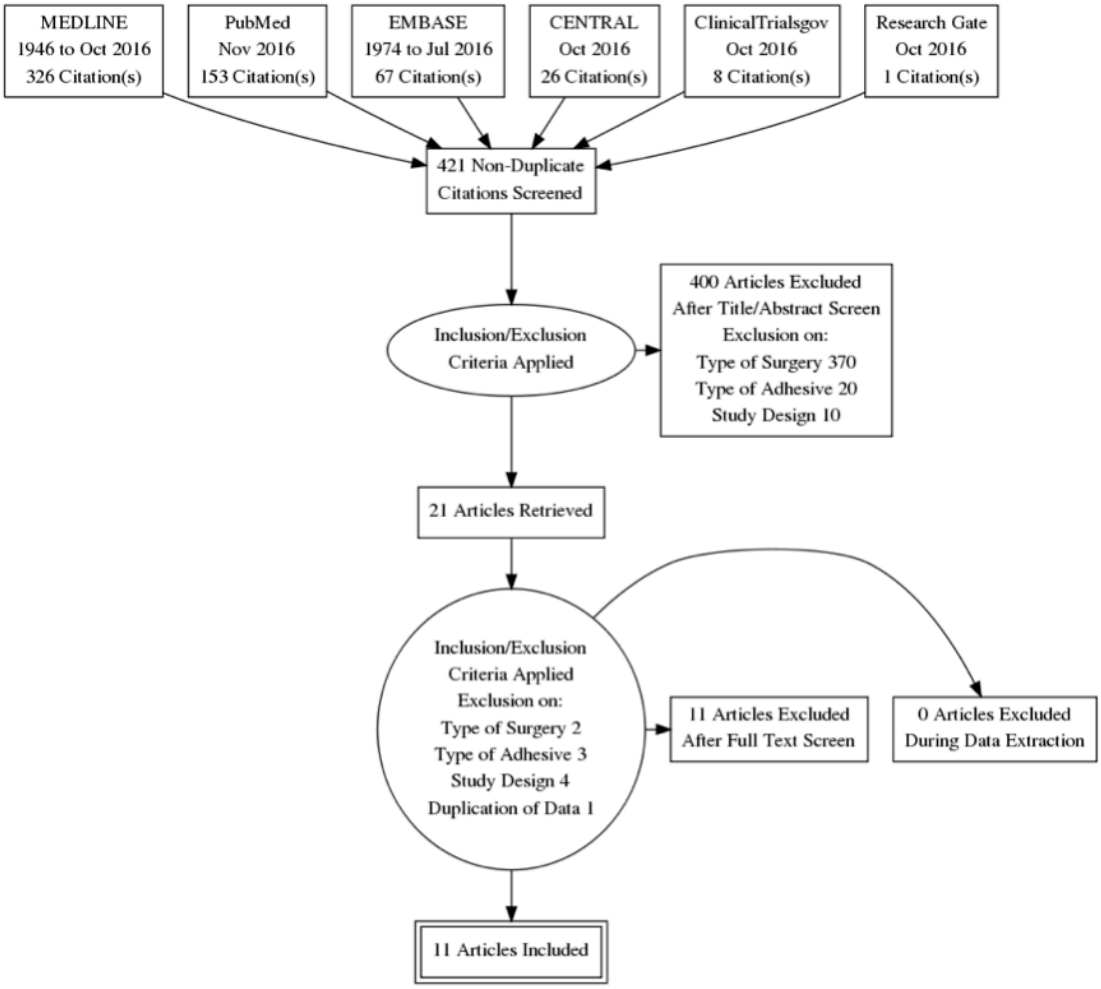


Figure 7 PRISMA diagram describing the screening process

Details of the included articles are provided in Table 5. Two trials looked at the use of FS in thyroidectomy (hemi- and total),(91, 92) 2 at total thyroidectomy with some form of neck dissection (Kim et al(93) included patients having central neck dissection whereas Vidal-Perez et al(94) included patients having central and lateral neck dissections), 1 at lateral neck dissection,(95) 1 at parotidectomy(96) and 5 at rhytidectomy.(79, 97-100) Only 6 of the included studies(79, 91, 93-95, 97) reported a sample size calculation and only 3 of these reached the planned sample size. Inclusion and exclusion criteria were broadly similar among all studies with all trials only including healthy adult patients and excluding patients who had previous

surgery to the area, were anticoagulated or had a bleeding/clotting disorder. Of note, only the trials by Hester et al used a low thrombin concentration FS (ARTISS) that is primarily designed to aid adhesion. All the other trials used high thrombin concentration FS that is primarily designed to aid haemostasis.

Table 5 Summary of included trials. Pts = Patients, FS = Fibrin Sealant.

Study	*Year*	*Surgery*	*Country*	*Planned sample size*	*Number randomised*	*No. of drop-outs*	*Reasons for drop-outs*	*Intention to treat analysis*	*Intervention*	*Control*
Hester et al(97) (phase II)	2013	Rhytidectomy	USA	40	46	1	Unclear	No	Artiss FS	No FS
Hester et al(79) (phase III)	2013	Rhytidectomy	USA	75	75	4	Screening failure, voluntary withdrawal	No	Artiss FS	No FS
Hornig et al(91)	2016	Thyroidectomy	USA	110	70	15	Voluntary withdrawal, deviation from protocol	No	Evicel FS	Saline Placebo
Huang et al(95)	2016	Lateral Neck Dissection	Taiwan	134	18	3	Neck wound communicated with upper aerodigestive tract, poor drain function	No	Tissucol FS	No FS
Kim et al(93)	2012	Thyroidectomy and central neck dissection	South Korea	72	78	0	-	-	Berplast P FS	No FS
Lee et al(98)	2009	Rhytidecomy	USA	-	9	0	-	-	Crosseal FS	No FS
Maharaj et al(96)	2006	Parotidectomy	Canada	-	60	10	Incomplete data or loss to follow-up	No	Tisseel FS	No FS
Marchac et al(99)	2005	Rhytidecomy	France	-	30	0	-	-	Tisseel FS	No FS
Oliver et al(100)	2001	Rhytidecomy	UK	-	20	0	-	-	Beriplast P FS	No FS
Uwiera et al(92)	2005	Thyroidectomy	Canada	-	56	0	-	-	Tisseel FS	No FS
Vidal-Perez et al(94)	2016	Thyroidectomy and neck dissection	Spain	60	60	0	-	-	Tissucol FS	No FS

Details of the risk of bias assessment are provided in Table 6. The overall quality of trials varied and many did not report complete methodological information to carry out a full assessment of risk of bias. In cases of incomplete information, authors were approached by email however only one responded. Key findings were that while random sequence generation was mostly adequately performed, such attempts at reducing selection bias were incomplete due

to the lack of adequate reporting of allocation concealment. None of the 5 trials in which patients dropped out after randomisation performed an 'Intention-to-treat' analysis. They were considered at high risk of attrition bias if the number of dropouts were unequal between the two groups of patients.(79, 91, 95-97) Four trials pre-registered their protocol on ClinicalTrials.gov so that a comparison between the planned outcomes and reported outcomes could be made and assessment of reporting bias possible.(79, 91, 93, 97) Several trials were industry funded but only the trials by Hester et al included authors who were employed by or were stockholders in the manufacturer (Baxter Healthcare).(79, 97)

Table 6 Risk of bias assessment of included trials. Green = low risk of bias, yellow = uncertainty, red = high risk of bias. A brief description of why the study was cat-egorised to a particular risk of bias is provided. FS = fibrin sealant, ITT = Intention to treat analysis

	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Conflict of Interest
Hester et al (2013)(97)	Predefined randomisation sequence	No data	Surgeon knew allocation prior to wound closure	Independent investigators	No ITT. But only one patient dropped out (equal for both groups)	Registered ClinicalTrials.gov	Industry funded; 2 authors employees &/or stockholders of Manufacturer
Hester et al (2013)(79)	Predefined randomisation sequence	No data	Surgeon knew allocation prior to wound closure	Not clear if investigators were different to surgeon	No ITT. But only four patients dropped out (equal for both groups)	Registered ClinicalTrials.gov	Industry funded; 2 authors employees &/or stockholders of Manufacturer
Hornig et al (2016)(91)	Computer generated random sequence	Allocation never revealed to surgeon as study staff closed the wound	Placebo control	Blinded assessors	No ITT and uncertainty about equality in both groups	Registered ClinicalTrials.gov	Industry funded
Huang et al (2016)(95)	Computer generated random sequence	No data	Surgeon knew allocation prior to wound closure	Blinded assessors	No ITT and uncertainty about equality in both groups	Pre-registered trial protocol not found	None declared
Kim et al (2012)(93)	Computer generated random sequence	Allocation concealed until the point of use in theatre	Patients blinded and surgeon blinded up to the point of use	Blinded assessors	No drop-outs	Registered ClinicalTrials.gov	None declared
Lee et al (2009)(98)	Random drawing of which side got FS e.g. flipping coin	No data	Surgeon knew allocation prior to wound closure	Blinded assessors	No drop-outs	Pre-registered trial protocol not found	Industry funded
Maharaj et al (2006)(96)	Sealed envelope	Envelope sealed until point of use	Patients blinded and surgeon blinded up to the point of use	Blinded assessors	No ITT and unequal drop-outs among groups	Pre-registered trial protocol not found	None declared
Marchac et al (2005)(99)	Not clear that patients were consecutive and method of randomisation was dubious	No data	Not clear when surgeon was unblinded	Surgeon assessed outcome	No drop-outs	Pre-registered trial protocol not found	None declared
Oliver et al (2001)(100)	Random drawing of which side got FS e.g. flipping coin	No data	Surgeon knew allocation prior to wound closure	Blinded assessors	No drop-outs	Pre-registered trial protocol not found	Industry funded
Uwiera et al (2005)(92)	Block Randomisation	No data	Not clear when surgeon was unblinded	Blinded assessors	No drop-outs	Pre-registered trial protocol not found	None declared
Vidal-Perez et al (2016)(94)	Sealed envelope	Envelope sealed until point of use	Patients blinded and surgeon blinded up to the point of use	Blinded assessors	No drop-outs	Pre-registered trial protocol not found	None declared

2.3.1 Primary outcomes

With regards to wound drainage all trials used a closed suction drain of varying calibre apart from Lee et al. who did not use any drains for rhytidectomy but rather applied a pressure bandage for 3 days.(98) Figure 8 shows the forest plot for all trials that provided enough data to perform meta-analysis on 'mean total drainage volume'. Similar surgical procedures are grouped together to enable sub-group analysis. Hornig et al(91) presented their data as median and IQR, the skewness was thought to be minimal and therefore the mean and SD was estimated.(89) Vidal-Perez et al presented their data as median with minimum and maximum values and the mean and SD was estimated.(90) The meta-analysis showed substantial statistical heterogeneity in all the sub-groups (thyroidectomy I^2 = 79%; surgery involving neck dissection I^2 = 94%) apart from in rhytidectomy (I^2 = 0%). There was a clear tendency for reduced 'mean total drainage volume' with FS in the overall analysis with a mean difference of 26.86ml (95% CI -43.41 to -10.31, p < 0.00001). Although this was statistically significant, the result needs to be interpreted with caution due to the substantial statistical and clinical heterogeneity of the studies (I^2 = 97%). The individual sub-group analysis concurs with the overall analysis, however for surgery involving neck dissection, the difference was not quite statistically significant (p = 0.08). The sub-group analysis of rhytidectomy shows a clear statistically significant benefit of FS reducing drainage volume with no statistical heterogeneity. The study by Maharaj et al was not included in the meta-analysis because they did not provide the standard deviation of the mean nor provide enough information to estimate it. The trial did however find that the mean total drainage volume in superficial and total parotidectomies was 41.3ml in the FS arm compared to control that was 65.3ml. This was a statistically significant difference (p = 0.02).(96)

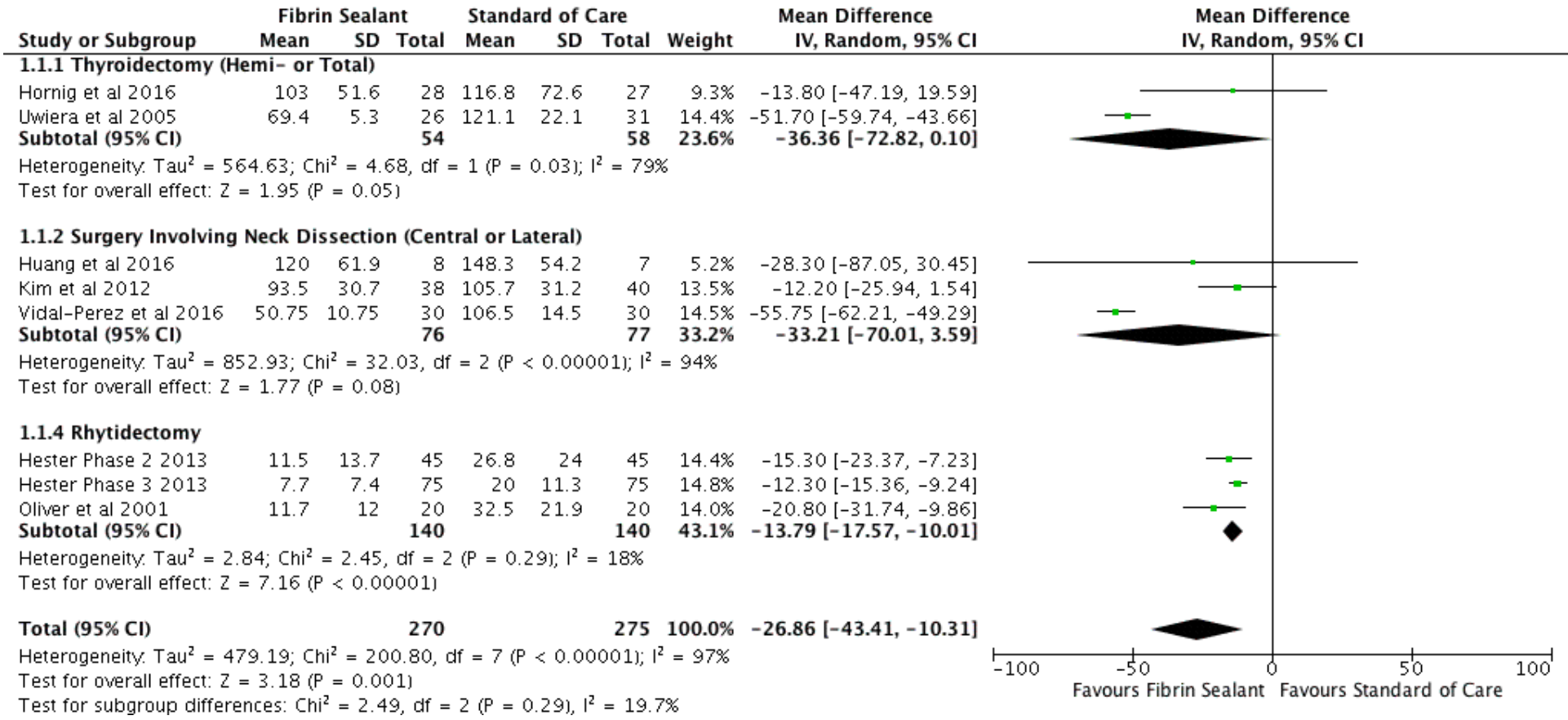


Figure 8 The effect of fibrin sealant on 'mean total drainage volume' (ml). Sub-group analysis of similar surgical procedures has been performed.

The meta-analysis on the retention time of drains (days) is shown in Figure 9A. This analysis includes 4 studies that looked at different surgical procedures and had different protocols for drain removal. Hornig et al removed the drain once it produced <10ml/8hrs; Huang et al <10ml/24hrs; Kim et al <20ml/24hrs; Vidal-Perez et al <20ml/24hrs. The overall analysis shows a tendency for FS to reduce the mean retention time of drains by 1.24 days (I^2 = 99%, 95%CI -3.32 to 0.85, p = 0.25) however there is substantial statistical heterogeneity and the difference is not statistically significant. This heterogeneity is primarily because the study by Vidal-Perez et al(94) very strongly favours the use of FS compared to the other studies. Studies involving rhytidectomy were not included because all drains were removed at approximately 24 hours. Maharaj et al(96) found that, for patients having parotidectomy, the FS group retained the drain for 25.6 hours and the control 30.4 hours; this study was excluded from meta-analysis because it did not provide the SD or p value other than to say it was not significant.

2.3.2 Secondary outcomes

The meta-analysis on 'hospital length of stay' in days is shown in Figure 9B. Overall, there was a tendency for FS to reduce hospital stay by 2.09 days (I^2 = 97%, 95% CI -5.18 to 0.99, p = 0.18) however this was not statistically significant and there was substantial statistical heterogeneity. Again, Maharaj et al was not included in the analysis because of missing information; they found that the mean time to discharge for patient having parotidectomy was 1.4 days in the FS group and 1.6 days in the control group, again this was not statistically significant (p value not provid

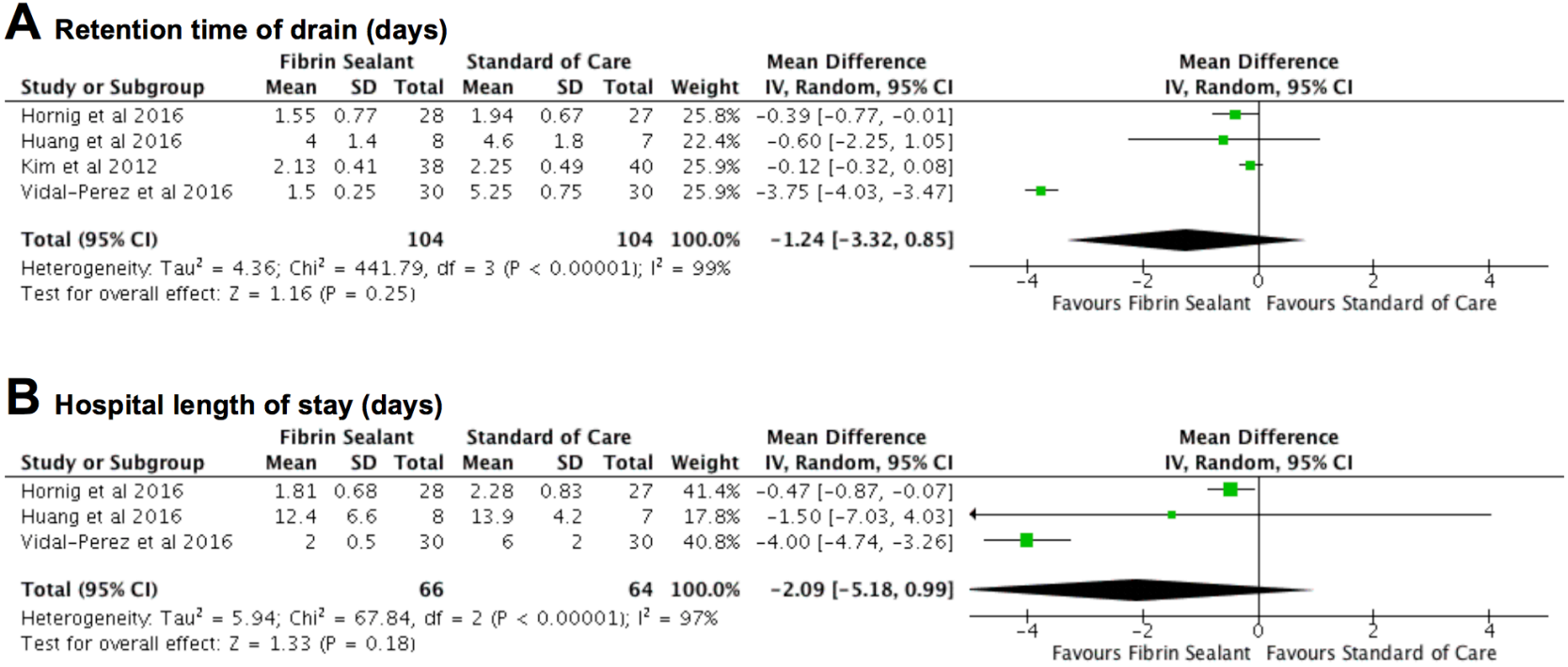


Figure 9 A) The effect of fibrin sealant on reducing the retention time of drains (days). B) The effect of fibrin sealant on hospital length of stay (days).

The meta-analysis of AEs (Clavien-Dindo grade II or worse) is shown in Figure 10A. This includes all surgical complications that required treatment within 30 days of the procedure and included haematoma/seroma formation that required invasive treatment, nerve palsies that required intervention, wound infections and ICU admission. There were no deaths reported in any study and there were no adverse reactions to FS (e.g. aprotinin sensitivity or surgical emphysema) reported. The meta-analysis shows that there was no statistical heterogeneity between trials (I^2 = 0%) and suggested that FS may be protective against developing a significant AE with a risk ratio of 0.69 but the 95% CI (0.35 to 1.38) includes values of risk ratio that could indicate harmful effect of either FS or standard care and so this result is inconclusive. Figure 10B shows the forest plot of a further analysis on the rate of haematoma/seroma requiring an intervention (e.g. aspiration or return to theatre). Again, there was no statistical heterogeneity (I^2 = 0%) and FS showed a tendency to reduce the risk of developing a haematoma or seroma with a risk ratio of 0.49 (95% CI 0.22 – 1.07). The effect of FS in reducing the rate of haematoma or seroma was not statistically significant (p = 0.07).

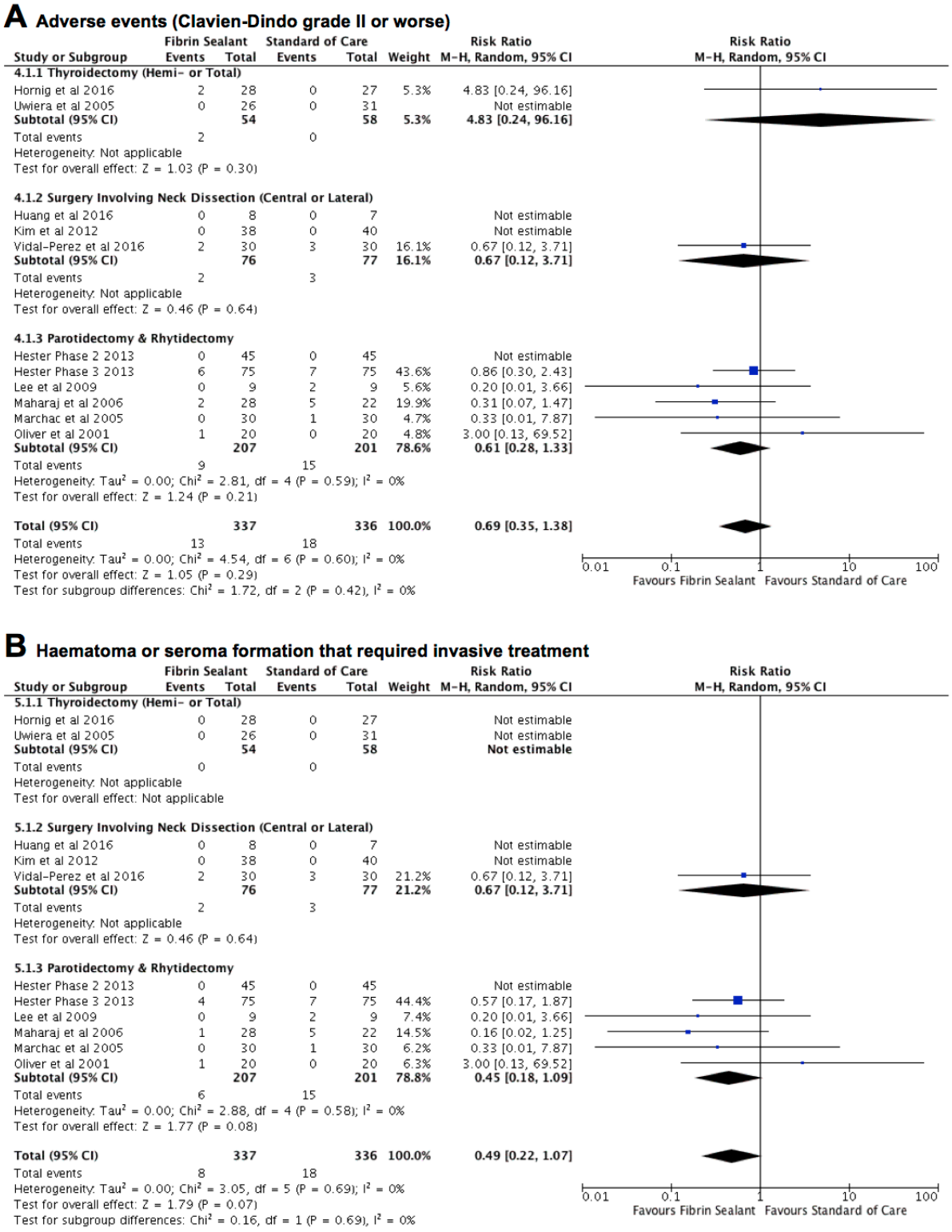


Figure 10 The effect of fibrin sealant on reducing complications. A) Shows the forest plot of all post-operative adverse events (Clavien-Dindo grade II or worse). B) Shows the forest plot of haematoma or seroma formation that required invasive treatment

Post-operative pain was reported in 3 studies that found no significant difference between FS and control.(94, 95, 97) All studies reported pain using visual analogue scales (VAS); only Vidal-Perez et al presented the data as a mean with SD, however they failed to specify at what point in the patient's pathway the VAS was measured. The other 2 studies presented the VAS in a bar graph format with no additional information. Unfortunately, due to the poor reporting of post-operative pain meta-analysis was not possible, however individually, no study found a statistically significant difference between the FS group and control. No trials assessed if FS improved the recovery of function using patient reported outcome measures. In terms of FS being acceptable to patients, only the trial by Huang et al reporting difficulties in recruitment.(95) Finally, Vidal-Perez et al was the only study to attempt a cost analysis. They found that the cost per patient in their institution was 377.72 Euro for the FS group and 1133.16 Euro for the control group. This was a significant difference ($p < 0.05$) and was primarily driven by the increased 'hospital length of stay' in the control group.

2.4 Discussion

This systematic review identified 11 RCTs that assessed the effect of FS on patients having soft-tissue surgery to the head and neck anatomical region. These studies were very heterogeneous in their quality, design and reporting making meta-analysis difficult to interpret and provide conclusive answers to the questions set out in the introduction. Whilst benefit from the inclusion of FS was a consistently apparent finding in all trials, this did not always translate into a difference in clinical outcome. Each operative sub-group is discussed in turn.

2.4.1 Thyroidectomy (Hemi- and Total)

There was substantial statistical heterogeneity in the sub-group analysis of thyroidectomy studies ($I^2 = 79\%$) in terms of 'mean total drainage volume'. This heterogeneity may have been because the differences in cut-off volume for drain removal (10ml/8hr for Hornig et al and

10ml/24hr for Uwiera et al) and the mean and SD was estimated for the study by Hornig et al.(89, 91) The 'mean total drainage volume' for thyroidectomy was significantly reduced by 36.36ml in the FS arm compared to control (95% CI -72.82 to 0.10, p = 0.05) however this is tempered by the high statistical heterogeneity. Hornig et al(91) and Uwiera et al(92) reported a "mean total drainage volume" ranging from approximately 70 – 120ml, this is contradictory to the meta-analysis by Woods et al(37) who demonstrated that not using drains was safe and may even be beneficial i.e. one would expect 70 – 120ml in the anterior neck to be clinically obvious and needing aspiration/evacuation. It is unclear if this disparity is simply due to the stimulating effect of a closed suction drain in the wound. As Woods et al(37) have shown that drains are not routinely required in thyroid surgery it is difficult to argue the case for using FS. The current meta-analysis shows that FS has potential benefits in reducing drainage volume but this has not translated into a significant difference in clinical outcome (both in the pooled and individual study analysis). The findings of this study offer little to change the practice of surgeons who already perform drainless surgery other than to say FS is safe to use. More evidence is required on the use of FS in patients who are at higher risk of complications (e.g. patients on anticoagulation).

2.4.2 Surgery involving neck dissection (central or lateral)

Overall FS had a tendency towards being beneficial in 'surgery that involved a neck dissection' in terms of reducing the 'mean total drainage volume' by 33.21ml (I^2 = 94%, 95% CI -70.01 to 3.59, p = 0.08). It is difficult to draw any conclusions regarding the clinical impact of this reduction in drainage volume because the result was not statistically significant and there was substantial statistical heterogeneity. This heterogeneity can be explained by the fact that the 3 studies included in this analysis incorporated different surgical procedures. Huang et al(95) just looked at lateral neck dissection, Kim et al(93) just looked at total thyroidectomy with central neck dissection and Vidal-Perez et al(94) looked at total thyroidectomy with central and lateral neck dissection. The degree of heterogeneity is compounded by the fact that Vidal-Perez et al(94) showed a significantly greater benefit of using FS compared to the other studies. Similar

effects of this study on the heterogeneity of meta-analysis can be seen in 'retention time of drains' and 'hospital length of stay' (Figure 9). It is possible that the estimation of mean and SD along with the subtle variation in drain removal protocol may have had a small part to play. Another explanation could be that FS is of greater benefit to patients who have a lateral neck dissection. Of all the procedures included in this review, lateral neck dissection is the most extensive and creates the greatest potential dead space. The surgery commonly involves large muscle belly exposure with dissection around large calibre vessels and carries with it, risks of major complication due in part to the proximity to the airway. Huang et al(95) did not show such a marked benefit from using FS, however their study was vastly underpowered due to problems with recruitment. The premise that FS is of greater benefit in patients having lateral neck dissection is supported by three non-randomised studies that both showed a clear benefit of using tissue adhesives (FS or autologous platelet and plasma adhesives). This is both in terms of total wound drainage and retention time of drains.(101-103)

2.4.3 Rhytidectomy & Parotidectomy

The evidence for the use of FS in parotidectomy and rhytidectomy seems more clear-cut. The meta-analysis shows that FS has a definite benefit in reducing wound drainage in rhytidectomy trials by approximately 13ml ($p < 0.00001$); this benefit also translates to a reduced rate of haematoma/seroma formation. The findings of this study agree with the findings of Killion et al(84), despite some differences in inclusion criteria of studies and statistical method, and support the use of FS in rhytidectomy.

Unfortunately the trial by Maharaj et al(96) on the use of FS in parotidectomies only provided enough data to include it in the meta-analysis on AEs and haematoma/seroma formation. If we analyse their results in isolation, they do support the use of FS in terms of reducing 'mean total drainage volume' and 'haematoma/seroma' formation. This is supported by the findings of Conboy and Brown who performed 21 parotidectomies using FS without a drain in a day surgery setting and reported no wound complications and found a health economic benefit.(104)

There is a need to substantiate these findings with a well-designed RCT comparing FS with no drain to standard of care with a drain. Having a third arm of this trial where patients are deprived of both FS and a drain is possible but may be controversial in terms of patient safety unless additional measures are taken e.g. pressure bandages are applied.

The types of FS used in each of the included studies is reported in Table 5. As already discussed, different FS preparations contain variable amounts of Thrombin, with a consequent impact on handling properties and balance between adhesion and haemostasis With reference to (sections 1.4.3 and 1.5.1). Only the two studies by Hester et al used a low Thrombin concentration FS. Both studies were strongly positive in terms of FS reducing mean total drainage volume after rhytidectomy. All remaining studies used high Thrombin concentration FS. The studies by Uwiera et al(92), Vidal-Perez et al(94) and Oliver et al(100) suggest that high Thrombin concentration FS can also reduce mean total drainage volume. This implies that whilst low Thrombin concentration FS may be effective at reducing drainage volume through closure of dead space, high Thrombin concentration FS may be effective at reducing drainage volume through haemostasis. Without a trial assessing the differing FS compositions, it is not possible to conclude which is the dominant factor.

It is important to clarify that only Woods et al(37) has provided robust evidence for the omission of surgical drains in thyroidectomy. Lee et al(98) used pressure bandages instead of surgical drains in both arms of their study on rhytidectomy; however not all head and neck procedures are amenable to the use of pressure bandages. Conboy and Brown(104) provide evidence through a small case series that surgical drains can be omitted in parotidectomy so long as FS is used. Therefore, any future trials comparing FS to standard of care without a drain need careful consideration with regards to patient safety, especially if the procedure in question is not amenable to pressure dressings e.g. lateral neck dissection. Furthermore, consideration should be given to how well a trial of this design is likely to recruit. Lack of surgeon equipoise is a recognised barrier to recruitment(105) and it is possible that many surgeons who routinely

use drains will lack equipoise.

Care should be taken when interpreting the numerical value of pooled mean differences shown in Figure 3 with regards to 'retention time of drains' (-1.24 days 95% CI -3.32 to 0.85) and 'hospital length of stay' (-2.09 days 95% CI -5.18 to 0.99). This is because of the substantial statistical heterogeneity and because the analysis was performed over different surgical procedures that may not be directly comparable. Instead, it is more appropriate to look at the 'relative' effect of FS on these outcomes. Overall, it is fair to say that the relative effect of FS is beneficial however not statistically significant.

The meta-analysis on AEs (Clavien-Dindo grade II or worse) demonstrated that FS is safe for use in the head and neck anatomical region and may have a protective benefit albeit not to a statistically significant level (I = 0%, RR 0.69, p = 0.29). The analysis on 'haematoma/seroma formation that required invasive treatment' showed that FS had a tendency for greater benefit (I^2 = 0%, RR 0.49, p = 0.07) but it was mainly the rhytidectomy and parotidectomy trials that contributed to this result. There were surprisingly few significant complications reported in the 'surgery involving neck dissection' studies. This can be explained by the fact that the studies excluded patients who were at high risk of complications (e.g. previous surgery, radiotherapy, bleeding disorders or anticoagulation).

2.5 Summary

To summarise the key findings of this study, each of the questions posed in the introduction has been addressed.

1) **Is there evidence that FS reduces the volume of wound drainage?** Overall FS has been shown to reduce the mean total volume drained (-26.86ml, 95% CI -43.41 to -10.31, P = 0.001, I^2 = 97%), however there is substantial statistical heterogeneity. Within the sub-group analyses 'thyroidectomy' and 'surgery involving neck dissection'

suffered from wide confidence intervals crossing the line of no effect. The evidence to support the use of FS in reducing the in mean total volume drained is stronger in the sub-group analysis of 'rhytidectomy'. Whilst overall FS reduced mean total volume drained, it debatable whether a difference of 26.86ml is clinically relevant. This is dependent on the circumstances in which FS is used. If FS is being used in surgery that creates a large area of dead space and requires prolonged drainage (e.g. ND), then a difference of 26.86ml is unlikely to be clinically relevant. However, if the area of dead space is relatively small (e.g. rhytidectomy), a reduction in drainage of 26.86ml could justify not using a drain at all.

2) **Is there evidence that FS reduces the time of surgical drain retention?** There was a tendency for patients who received FS to have reductions in the retention time of drains however this was not statistically significant. Most studies found that this reduction was less than 0.5 days and so did not translate to a clinically significant outcome. One study found that FS reduced the time of drain removal by 3.75 days which is clinically significant[15], however no other study reproduced this outcome leading to the substantial statistical heterogeneity (I^2 = 99%) as shown in Figure 9A.

3) **Is there evidence that FS reduces the time to discharge or time to being declared surgically fit for discharge?** Again, there was a tendency for FS to reduce the hospital length of stay but this was not statistically significant and hampered by substantial statistical heterogeneity (Figure 9B).

4) **Is there evidence that FS reduces the rate of clinically significant AEs defined as Clavien-Dindo(23) grade II or worse, or the rate of haematoma/seroma formation?** There was a tendency for FS to reduce the rate of clinically significant AEs (Figure 10A) albeit not to a statistically significant level. The evidence for FS reducing the rate of haematoma or seroma was stronger (Figure 10B). It is important to note that many studies had no complications in either arm. This is likely to be a consequence of a conscious decision by study designers to exclude patients at increased

risk of complications.

5) **Is there evidence that FS reduces post-operative pain?** Meta-analysis of post-operative pain was not possible due to the differing ways that studies reported it. Of the 3 studies that did report pain, none found that FS made a statistically significant difference.
6) **Is there evidence that FS allows a quicker return to normal function as documented by patient reported outcome measures?** None of the studies in this review looked at the effects of FS on health-related quality of life and whether it expedited the return to normal function.
7) **Is FS considered to be an acceptable intervention by patients?** All studies apart from 1 found that FS was an acceptable intervention for patients. This study reported difficulties in recruitment but did not explain why patients were averse to participation.
8) **Is FS a cost-effective intervention?** No studies performed detailed cost analyses. One study reported a crude cost-benefit analysis and found FS resulted in a saving of 755 Euro per patient driven by reduced hospital length of stay.

2.6 Conclusion

In conclusion this systematic review has found that the evidence for the use of FS in soft-tissue head and neck surgery is encouraging. However, the value of these results is constrained by heterogeneous, sometimes poor, methodology and reporting of trials leading to necessary caution when interpreting. As such the ability for robust conclusions to be drawn from meta-analyses are necessarily limited. All the trials included in this systematic review excluded patients who were at increased risk of developing complications. Given that we are faced with an ageing population who may have multiple co-morbidities, future trials should include these patients so that our understanding of the role of FS in head and neck surgery may improve. Further clinical trials incorporating robust methodology are needed, this is particularly the case with regards to

lateral neck dissection where there is a paucity of randomised data and where the potential for greatest benefit exists, through avoidance of severe complications and reduction in hospital length of stay.

2.7 Influence of this work on future trial design

Through the process of conducting this systematic review the design of any future trial can be improved to make the results more applicable to a broader range of surgeons and policy makers. Key areas for improvement are discussed below.

1. **Conducting the study over multiple centres.** All the studies included in the systematic review were single-centre studies. To make the results more generalisable, including multiple centres would make the trial more pragmatic in design and allow a greater impact of the findings on clinical practice.

2. **Broader inclusion criteria.** Many of the included studies excluded patients that were deemed to be at high-risk of complications. With the incidence of HNC increasing in an ageing population with multiple co-morbidities, this eligibility criteria may not accurately represent the patients it will be used on in routine clinical practice.(1, 2) Furthermore, excluding patients at high-risk of complications may overestimate the benefit of FS.

3. **Computer generated randomisation sequences.** Like many of the included trials, using computer generated randomisation sequences is a considerably more robust approach to minimising selection bias when compared to techniques like sealed envelopes.

4. **Revealing the allocation at the point of wound closure.** Surgeons who know the allocation prior to starting the operation have scope to introduce performance bias. This can be minimised by revealing the allocation intra-operatively and at the point of

wound closure. However, consideration needs to be given to including mechanisms to monitor adherence to this process.

5. **Consider using a low Thrombin concentration FS.** Low Thrombin concentration FS has been engineered specifically to aid adherence of tissues and close dead space.(51) All the trials that have used this type of FS have shown encouraging results.(78-81) Whilst some trials that used a high Thrombin concentration FS have also shown benefit,(92, 94, 100) the extra time afforded by the delayed onset of polymerisation is likely to improve the ease of use for the broad range of surgeons recruiting to a multicentre trial.

6. **Selecting an appropriate control.** Apart from Hornig et al all the included trials used standard of care without FS as the control arm. Hornig et al opted for a saline placebo control. Superficially this seems like a more robust control because surgeons are also blinded (double-blind). However, the consistency of saline is different to FS and it is very likely that surgeons can tell the difference both when the solution is viewed in the syringe and when it is applied to the wound. In order to produce an appropriate placebo a safe product that has a very similar consistency and appearance is required. Although placebo control might represent an ideal inclusion for trial design, production would likely be prohibitively expensive. Accepting that it might be difficult to justify such costs, alternative means of ensuring validity of outcome (such as assessor blinding) could be employed.

7. **Outcome assessors and patients should be blinded.** This is required to minimise detection bias and should be considered a minimum requirement. Because the patient is under general anaesthesia blinding them to the allocation is relatively straightforward. It is important to select outcome assessors who are not present in theatre while the intervention is being administered.

8. **Performing an intention-to-treat analysis.** This is important to account for attrition bias that occurs when unequal numbers of participants that do not complete the trial. This will provide useful information to surgeons in policy makers when deciding whether to adopt FS in their practice.

9. **Minimising conflicts of interest.** The studies by Hester et al were industry funded and included authors who were stakeholders in the product. Whilst there is no evidence that the studies were conducted unethically, conflicts of interest do sow seeds of doubt in the reader thereby minimising the impact of the work.

These points for consideration demonstrate that undertaking the systematic review prior to designing a future trial is a valuable process. The justification for a future definitive RCT is discussed in detail in Chapter 3.

Chapter 3. RATIONALE FOR THESIS

3.1 Rationale for Randomised Controlled Trial

To date there are only two RCTs that have assessed the role of FS in lateral ND (as opposed to central ND).(94, 95) These trials have randomised a total of 75 patients between them. Both trials were single centre studies conducted in specialised healthcare settings with only 1 or 2 surgeons operating on all the patients. This implies that the trials were more on the explanatory end of the continuum and raises doubt regarding the external validity of the findings and whether they are applicable to UK surgeons working within the NHS. Furthermore, the outcome measures for both trials focused on drainage volumes or hospital length of stay; whilst these are important outcomes for service providers, there is currently no published evidence that these outcomes are meaningful to patients. Huang et al failed to recruit adequate numbers of patients due to "challenging recruitment" but provided no further detail on the specific challenges.(95) Vidal-Perez et al was a relatively well conducted trial that was deemed to be at low risk of bias and demonstrated very positive outcomes in favour of FS.(94) However, the trial should be considered an outlier in the meta-analysis undertaken in Chapter 2. Whilst it demonstrated evidence of efficacy, the results have not been reproduced by other authors. Furthermore, the trial only included patients with thyroid cancer who are unlikely to be representative of all head and neck surgery patients. Olson et al retrospectively reviewed the National Cancer Database and demonstrated that the incidence of thyroid cancer is increasing within the US and possibly related to an evolving patient demographic.(106) The increased incidence is primarily driven by the early diagnosis of papillary thyroid cancers and associated with patients who have better access to healthcare and higher socioeconomic status.(106) This patient demographic is not likely to be representative of patients with mucosal HNC which has a higher incidence in deprived populations.(1)

In 1967 Schwartz and Lellouch stated that explanatory trials confirm a clinical hypothesis whereas pragmatic trails inform clinical or policy decisions.(107) More recently Zwarenstein et al published recommendations to improve the reporting of pragmatic trials. Table 7 summarises the key differences the authors described between trials that adopt an explanatory and pragmatic attitude.(108)

Table 7 Key differences between explanatory and pragmatic trials taken from Zwarenstein et al.(106)

	Explanatory attitude	**Pragmatic attitude**
Question	Efficacy: can the intervention work?	Effectiveness: does the intervention work when used in normal practice?
Setting	Well resourced, 'ideal' setting	Normal practice
Participants	Highly selected; poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibly as it would be in normal practice
Outcomes	Often short-term surrogates, or process measures	Directly relevant to participants, funders, communities and healthcare practitioners
Relevance to practice	Indirect: little effort is made to match the design of the trial to the decision making needs of those in the usual setting in which the intervention will be implemented	Direct: the trial is designed to meet the needs of those making decisions about treatment options in the setting in which the intervention will be implemented

The PRECIS-2 tool provides a framework for assessing where a trial design lies on the explanatory-pragmatic continuum.(109) The assessment of trial design is based on nine domains

using a five-point Likert scale, 1 being 'very explanatory' and 5 being 'very pragmatic'. The nine domains are as follows:

1. **Eligibility criteria.** A pragmatic approach would have broad inclusion criteria and minimal exclusion criteria such that participants are representative of patients that would receive the intervention in usual care. An explanatory approach would exclude participants who are unlikely to respond or adhere to the intervention/study protocol or exclude participants based on demographics or tests that are not applied in usual care.(109)
2. **Recruitment.** A pragmatic approach would recruit participants from a normal clinical environment with no overt recruitment effort. Overt recruitment efforts such as searching medical records for eligible patients, sending out letters, using a media campaign or providing cash incentives would move the study design more towards the explanatory end of the continuum.(109)
3. **Setting.** A pragmatic approach would mirror the setting where the results of the trial will be applied. Characteristics include geography, healthcare system and demographic of the population. Running the trial in a single centre or only in academic/specialist centres when the results are meant to be applicable to all centres makes the trial more explanatory.(109)
4. **Organisation.** A pragmatic approach would mirror how care is organised and delivered in usual care and not make use of extra resources. Increasing staffing levels to deliver the intervention, providing significant additional training, requiring investigators to have a minimum level of experience or certification all make the design more explanatory.(109)
5. **Flexibility of delivery.** A pragmatic approach would mirror how the intervention will be delivered in usual care and allow investigators the flexibility to deliver it as they see fit. Having a highly specified protocol-driven intervention and having measures in place to monitor compliance of those delivering the intervention would make the trial more explanatory.(109) Within the context of surgical trial design, it is considered important

to maintain the fidelity of the 'core steps' of the intervention to ensure it is delivered in a standardised fashion. Whilst this concept is at odds with a truly pragmatic trial design, it is possible to vary the degree to which the fidelity of the intervention is monitored.(110)

6. **Flexibility of adherence.** A pragmatic approach would allow participants to flexibly engage with the intervention as they would in usual care. Excluding participants who may not adhere to the intervention, withdrawing participants that do not adhere to the intervention well enough and introducing measures to monitor participant adherence would all make the trial more explanatory.(109)
7. **Follow-up.** A pragmatic approach would avoid extra visits beyond those required in usual care. The most pragmatic designs often avoid any follow-up altogether and collect data via other means e.g. electronic medical records. More frequent follow-up than usual care, contacting participants if they do not attend appointments, collecting more extensive data than would be typical outside the trial and having longer follow-up appointments all make the design more explanatory.(109)
8. **Primary outcome.** A pragmatic approach would select an outcome that is significant to patients as well as being relevant to commissioners. It is also important to measure the outcome as it would be measured in usual care. Selecting surrogate or composite outcomes, having central adjudication of the outcome or selecting an outcome that is more important to providers than patients make a trial more explanatory.(109)
9. **Primary analysis.** A pragmatic approach would be to employ an 'intention-to-treat' analysis using all available data and not making special allowances. Adopting a 'per protocol' analysis makes the trial more explanatory.(109)

In order to better understand the applicability of the current trials-based evidence for FS in ND, the PRECIS-2 tool has been used to analyse the design of the trials by Huang et al and Vidal-Perez et al.(94, 95) The PRECIS-2 wheel in Figure 11 summarises the findings.

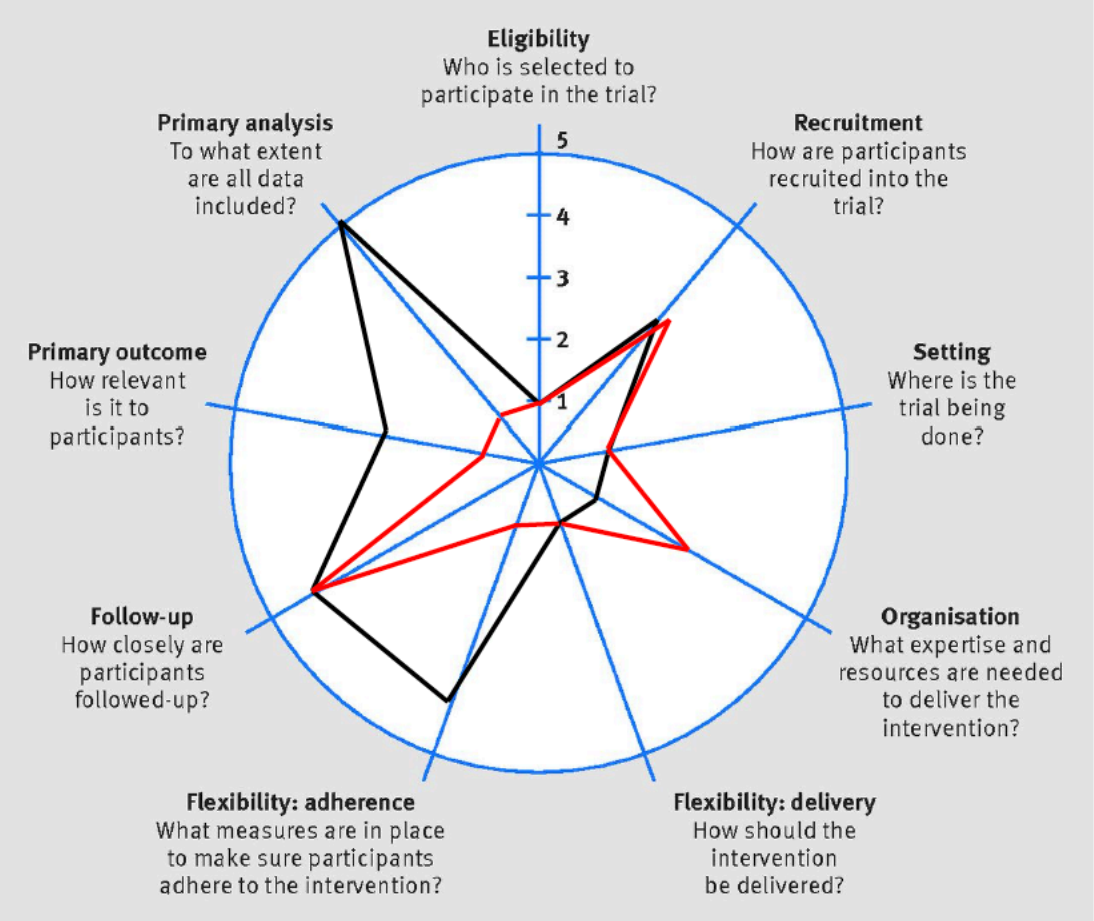


Figure 11 PRECIS-2 wheels for existing trials evaluating Fibrin Sealant in Neck Dissection. Black line – PRECIS-2 wheel for Vidal-Perez et al.(92) Red line – PRECIS-2 wheel for Huang et al.(93)

The black line in Figure 11 represents the trial by Vidal-Perez et al(94) and demonstrates the trial had a mixture of pragmatic and explanatory design features. Eligibility was restricted to patients who were medically fit and had a BMI<30 making it a very explanatory design feature. Recruitment was from consecutive patients attending a clinic with no overt recruitment effort. It falls short of maximum points because participants were recruited from only one clinic and no information is provided regarding the number of eligible patients who turned down participation. In terms of setting, the trial was conducted in a single specialist centre by two experienced surgeons making it a very explanatory design feature. Whilst it appears that no additional

organisational features were included in the trial design, only 2 surgeons who had experience of over 1000 cases operated on participants. Requiring the surgeons to have this level of experience is an explanatory design feature. Flexibility in delivery of the intervention was very explanatory because both surgeons followed a strict surgical protocol outlined in the paper. Flexibility of adherence was pragmatic since patients were not excluded based on their likelihood to adhere to the trial. Similarly, no patients were reported to have been withdrawn from the trial due to a lack of adherence. As the intervention was administered only once during surgery and data was collected during the patient's hospital admission, there was very little opportunity for non-adherence to trial processes hence it fell short of the maximum 5 points. The Follow-up arrangements were pragmatic because no extra visits were required for the trial and no extra data was collected beyond usual care. It falls short of maximum points because the follow-up period was incredibly short (until discharge from hospital). The primary outcome was length of hospital stay which is a very short-term metric. Whilst reducing hospital admission benefits both patients and commissioners of care, there is no reference to suggest reducing length of hospital admission was the most important outcome for patients. Primary analysis scored maximum points because there were no dropouts, and an 'intention-to-treat' analysis was performed.

The red line in Figure 11 represents the trial by Huang et al(95) and demonstrates a predominantly explanatory trial design. Eligibility was very explanatory because patients who were not between the age of 20-80 years and patients who had coagulation disorders, previous treatment to the neck, or a reluctance to participate were excluded. Like the trial by Vidal-Perez et al, no overt recruitment effort is reported but recruitment was from a single clinic. In terms of setting, the trial was conducted in a single centre and participants were operated on by a single surgeon. This is clearly a very explanatory design feature. Organisation had both pragmatic and explanatory features because no significant extra organisational features were employed but slightly more data than usual care was collected in terms of pain and a very specific analgesia regimen was employed. Flexibility of delivery was limited to the technique of a single

surgeon and therefore very explanatory. Flexibility of adherence was also very explanatory because patients who were unlikely to adhere to the trial were excluded and participants who later did not adhere to the trial were also excluded. Follow-up was mainly pragmatic because no extra visits were required, but like the trial by Vidal-Perez et al(94), the follow-up period was incredibly short. The primary outcome measure was post-operative drainage volume. This is an explanatory outcome measure as it may be considered a surrogate for overall wound healing and there is no evidence that volume matters to patients. Primary analysis was performed on a 'per protocol' basis making it explanatory in nature. Whilst both trials had elements of pragmatism, areas where they could be more pragmatic are in the domains of eligibility, setting and flexibility of delivery.

Ultimately the aim of a future definitive DEFeND trial would be to guide clinical decision making. Therefore, based on the considerations detailed above, a pragmatic trial design seems the most obvious choice. If one assumes that Huang et al(95) and Vidal-Perez et al(94) also wished for their trials to guide clinical practice, why did they opt for such explanatory designs? The answer to this question is likely to be multifactorial and may include the following reasons:

1. Explanatory trials tend to be smaller, more rapidly conducted and therefore cheaper.(111)
2. A desire to produce a positive trial outcome. Reporting bias arises when the dissemination of research findings is influenced by the nature and direction of results. Statistically significant results that indicate an intervention works are more likely to be published and cited.(88) Explanatory trials are more likely to overestimate benefit and underestimate harm.(112)
3. The authors may lack understanding of the explanatory-pragmatic continuum and how discerning clinicians and policy makers are likely to interpret the results before implementing change in their own practice.
4. The explanatory trial was performed to test efficacy of FS prior to a planned pragmatic trial that is yet to be undertaken. This seems unlikely as both studies were published

several years ago and, at the time of writing, neither authors have registered further trials.

5. Not all research questions are suitable for pragmatic trials. As discussed above, the standardised delivery of a surgical intervention does encounter some conflicts with a truly pragmatic trial design e.g. the balance between flexibility of delivery and fidelity of the intervention. This point is discussed further in the chapter.

Given the nature and quality of the current evidence for FS in ND, there are essentially two options to move forward. The first option is to carry out further explanatory trials to prove 'efficacy' before undertaking a larger pragmatic trial to prove 'effectiveness'. This may be a valid approach because currently there are no trials that assess the efficacy of low-thrombin concentration FS in ND. The second option is to progress to a more pragmatic trial design. As mentioned previously, pragmatic trials are more likely to inform clinical decision making and commissioners of care. As discussed previously (Chapter 1. and Chapter 2, FS are products with a well-established safety profile that are widely used across several areas of surgery and already authorised for use by the FDA, MHRA and EMA. They are no longer considered novel investigational products and therefore it is possible to utilise existing data to inform a more pragmatic design which will ultimately be more informative. Whilst in theory the argument for a pragmatic trial seems strong, trials assessing surgical interventions may present challenges to this endeavour.

Pragmatic trials require participants to be representative of patients who would receive the intervention in usual care. However, recruitment to surgical trials is rarely even close to 100%.(105) In an observational study of surgical RCTs registered on ClinicalTrials.gov, recruitment problems are the main reason why approximately 20% of surgical RCTs are stopped early.(113) Therefore, depending on the recruitment rate and the profile of patients who decline trial participation, the trial's recruitment may not be truly representative of the population. Design features such as minimisation of eligibility criteria, reduction in number and complexity of

study visits, reduction of research burden will improve participation but are only partial measures.(114)

Multicentre trials need local investigators to take responsibility for recruitment, treatment, and follow-up. Many clinicians outside of academic centres do not participate in clinical trials. This means that patients being treated in the majority of (non-academic) centres will not have the option to participate or would need to have care transferred to a recruiting centre. This will further reduce the patient pool and hinder the ability to deliver a truly pragmatic trial.(114)

In a pragmatic surgical trial, the intervention should be delivered within a usual care setting by surgeons and ancillary staff with typical expertise and experience. This means that a pragmatic trial design needs to allow a certain level of flexibility to deliver the intervention whilst still retaining trial rigor. However, a trial that is dominated by poor adherence to the protocol, particularly in the 'core steps' of the intervention, becomes of decreasing value.(110) The trial design needs to strike a balance between providing enough flexibility that the trial is considered pragmatic whilst also providing investigators with enough guidance to maintain a degree of fidelity and standardisation of the intervention.

Follow-up in pragmatic trials needs to be as unobtrusive as possible, ideally bypassing the patient and collecting data from electronic health records. However, the granularity of data in electronic records beyond major clinical events such as death, readmissions and returns to theatre is often sub-optimal and cannot be relied upon.(114) Most patients who undergo surgery are followed-up routinely by their surgical teams. Therefore, limiting data collection to these visits seems the most prudent approach without becoming burdensome on enrolled patients. Pragmatic outcomes should be important to patients and, in addition to major clinical events, may often include outcomes relating to symptoms, disability and quality of life. However, these metrics are seldom consistently recorded in routine practice and require engagement with the patient.(114) Using web-based forms or apps on hand-held devices may reduce

research burden and the number of visits required but may also exclude patients who are not computer literate or do not have access to the necessary electronic devices.

Another challenge related to undertaking a pragmatic trial of FS in ND is the timing of the trial. Appropriate timing of surgical trials is often considered a key stumbling block in determining equipoise.(115) Buxton's law states that "it is always too early for rigorous evaluation until suddenly it is too late".(116) This relates to the phenomenon that a new surgical technique is initially unstable and subject to refinement as the surgeon learns. The point at which the technique does stabilise, the surgeon may become convinced of it's worth and lack the equipoise to randomise. This phenomenon can be related to the proposal for a pragmatic trial because FS is "CE" marked, FDA approved and has been available to surgeons for several years but is not widely used in ND. This demonstrates some degree of community equipoise, but individual surgeon equipoise may be more problematic. Based on Buxton's law, some surgeons may lack equipoise on an individual basis because they have had time to evaluate FS in their own practice. Demonstrating community equipoise means that a future trial has met an essential criterion to justify ethical randomisation however, there is uncertainty regarding the willingness of individual surgeons to recruit.

In summary, this discussion has demonstrated that the current evidence for FS in ND falls towards the explanatory end of the continuum and lacks necessary external validity and generalisability. Whilst there is evidence in support of FS as being of potential benefit to patients/healthcare systems, there is a need for a future RCT that is pragmatic in nature to better inform clinicians and commissioners of care. A truly pure pragmatic design may not be possible or suitable for this specific research question, however, there is certainly scope to make the design more pragmatic when compared to existing/prior trials undertaken in this space. This future trial would then be more applicable to clinicians working in a similar healthcare environment.

3.2 Rationale for Pilot & Feasibility Study

3.2.1 Definitions

The NIHR define pilot studies as smaller versions of the main study to test whether the components work well together and are primarily focused on processes.(117) It defines feasibility studies as those that are done to answer whether the main study can be done.(118) The conceptual framework by Eldridge et al provides a more fluid definition where the relationship between pilot and feasibility studies is not mutually exclusive. The framework is summarised in Figure 12 and describes feasibility as an overarching concept of which three distinct types of study are a subset. These are: non-randomised pilot studies; feasibility studies that are not pilot studies; randomised pilot studies.(119)

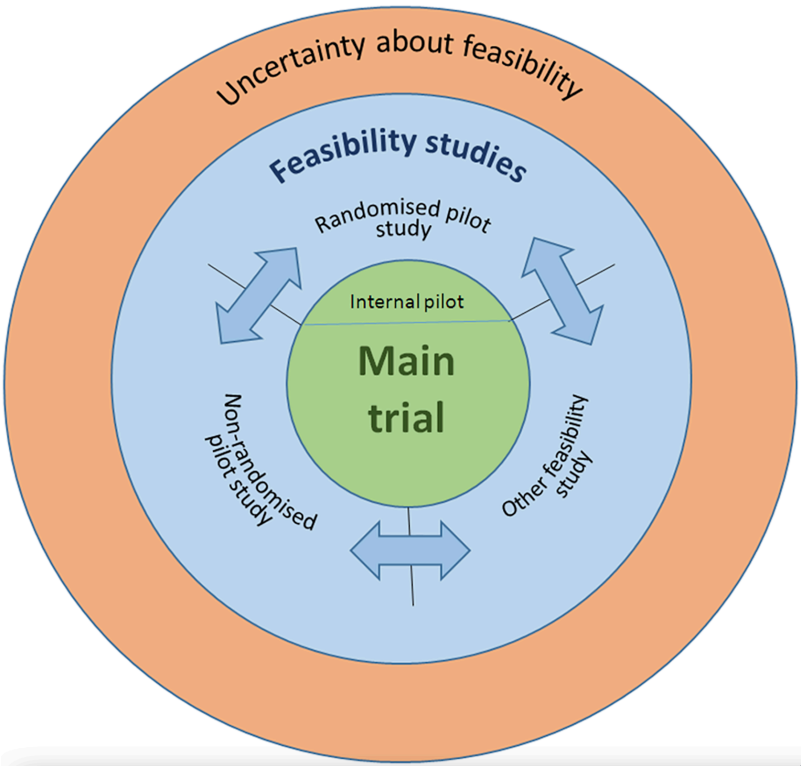


Figure 12 Conceptual framework of pilot and feasibility studies by Eldridge et al.(117)

Randomised pilot studies are those studies in which the future RCT is conducted on a smaller scale (piloted) to see if it can be done. These studies reflect the design of the definitive trial but, due to uncertainty, may explore a different approach to specific processes. Non-randomised pilot studies are those in which the intervention and associated processes are piloted without randomisation. This may include a single arm design to assess the processes associated with the intervention only. Feasibility studies that are not pilot studies are those that answer whether components of a definitive trial can be done without necessarily implementing the intervention or its associated processes.(119)

3.2.2 Role of pilot & feasibility studies

Pilot and feasibility studies (PFS) have an important role and, if used appropriately, can provide important evidence that informs the design, planning and justification of a definitive trial. Furthermore, they may prevent research waste by identifying problems that may limit the successful delivery of a definitive trial.(120, 121)

It is well documented that surgical trials are challenging and present issues beyond those encountered in drug trials. These may include uncertainties around equipoise and recruitment (as mentioned in the last section), the nature of the intervention itself and the most appropriate outcome measure(s).(122, 123) Recently published research into the value of surgical PFS protocols has demonstrated that the full potential of these studies has not been realised within surgical research.(124) Furthermore, there is a lack of understanding regarding the role of PFS with many authors conducting formal hypothesis testing. An incomplete understanding of all the uncertainties may be demonstrated in the design of PFS in some funding applications. The end points of these studies are often skewed towards the priorities of funders (e.g. recruitment) without giving necessary thought to the uncertainties that are specific or unique to the study. This research also highlighted issues surrounding the perceived lack of value of PFS amongst surgeons and journal editors.(124)

Some guidance on the role of PFS within surgical research can be gleaned from strategic guidance such as the IDEAL framework. IDEAL began with a series of meetings at Balliol College between 2007 – 2009 to discuss the specific challenges of surgical innovation.(125) This led to a landmark publication in the Lancet in 2009.(126) The IDEAL Framework is now a widely accepted set of recommendations that describe the stages of surgical innovation. These recommendations formalise an approach to surgical research that accommodates the complexities with a view to improving quality. These stages are: Idea, Development, Exploration, Assessment, and Long-term study.(126) Figure 13 summaries the stages. The concepts and recommendations of IDEAL were later extended in 2019 to provide more practical details for investigators wishing to implement them.(127)

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; complete information for non-RCT participants	Description; audit, regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); diseased based (diagnostic)	RCT with or without additions/ modifications; alternative designs	Registry; routine database (eg, SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle-term and long-term outcomes; patient-centred (reported) outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video[6]	Tissue engineered vessels[7]	Italian D2 gastrectomy study[8]	Swedish obese patients study[9]	UK national adult cardiac surgical database[10]

RCT=randomised controlled trial. SCOAP=Surgical Clinical Outcomes Assessment Programme. STS=Society of Thoracic Surgeons. NSQIP=National Surgical Quality Improvement Program. NOTES=natural orifice translumenal endoscopic surgery.

Table: **Stages of surgical innovation**

Figure 13 IDEAL Framework. Stages of surgical innovation. (Figure taken from McCulloch et al (124))

If using the framework to guide further evaluation of FS in ND, it is important to identify where the current research sits within the framework. IDEAL stage 1 describes the first use of a new procedure or device in a patient. This usually takes the form of a small case series that uses safety and technical success as its outcomes.(127) Given that FS are "CE" marked and FDA approved for human use, the criteria for IDEAL stage 1 have already been met. Stage 2a describes the iterative modifications to the technique towards a stable version i.e. when and why modifications to the technique or indications occurred to avoid repetition of failures.(127) The criteria for Stage 2a (development) appear to have been met because several FS products have been used by surgeons for several years and the technique for use is clearly described by the manufacturers. Additionally, Summary of Product Characteristic (SmPC) documents are available for a wide range of FS products on the market and provide detailed information on composition, dose, pharmacology, preparation, administration and safety.(51) In the context of stage 2a, the development of FS seems more akin to drug development than the development of a novel surgical technique.

A stage 2b study should address any uncertainties that might compromise the successful delivery of a future IDEAL stage 3 RCT.(127) Based on this definition, most PFS (including DEFeND) sit comfortably within this category. A possible exception being feasibility studies that are not pilot studies where the primary objective is to refine and stabilise a novel intervention i.e. demonstrating that a novel intervention *can* be delivered appropriately within a definitive trial.

The current best evidence for FS in ND includes two small single-centre explanatory trials that lack the external validity to inform wider clinical decision making and policy.(94, 95) Whilst these trials do *assess* the efficacy of FS in ND, it is debatable whether they meet the criteria of an IDEAL stage 3 assessment. Based on the IDEAL framework and updated recommendations published in 2019, a stage 3 assessment should include more patients with broader eligibility criteria and more surgeons e.g. an early majority.(127) This provides further support for

a more pragmatic trial design. Whilst these trials may not stand up to scrutiny in terms of a stage 3 assessment, they do provide some information regarding feasibility. By virtue of their existence, they teach us that a definitive trial *can* be done and is therefore feasible according to the NIHR definition.(118) Unfortunately, their reporting is not robust or detailed enough to address uncertainties around the feasibility of specific design features and the processes required for the delivery of a more pragmatic trial design. On this basis a further PFS is indicated, however, the type of PFS is dependent on the specific uncertainties that need to be addressed. The anticipated uncertainties of running a more pragmatic RCT on the role of FS in ND are summarised below. This is based on: the systematic review reported in Chapter 2(82); a review by Cook that described the challenges of surgical trials in general(115); a survey by Kaur et al that reported the barriers to recruitment for surgical trials in head and neck oncology.(105)

3.2.3 Barriers to an immediate and definitive DEFeND trial

3.2.3.1 Recruitment

As previously mentioned, the timing of DEFeND may have implications on individual surgeon equipoise and their willingness to recruit patients. Additionally, Kaur et al reported that the most significant barrier to recruitment in head and neck surgery trials was 'patient refusal because of treatment preference'.(105) There is evidence that this treatment preference is related to the way surgeons convey equipoise and allow their own personal bias to influence the patient's decision.(128) Therefore, uncertainty surrounding individual surgeon equipoise and their ability to convey equipoise is likely to influence recruitment to DEFeND.

A pragmatic trial design should include multiple centres with varying levels of expertise such that an assessment of 'real-world' effectiveness can be made.(129) All previous studies of FS in ND have been single-centre, furthermore, how centres with limited experience in recruiting to surgical trials will perform is unknown. To this end the DEFeND PFS needs to address these

uncertainties by recruiting across multiple centres with surgeons of varying levels of expertise in delivering the intervention and recruiting to surgical trials.

3.2.3.2 Inclusion criteria

In keeping with a pragmatic trial design, eligibility criteria need to be broad whilst also acknowledging that not all NDs are equal. Some NDs are part of complex operations that require free-flap reconstruction. Free-flaps are technically demanding and of great importance to the patient's wound healing and function. Free-flap failure is associated with returns to theatre, prolonged hospital admission, significant morbidity, and psychological distress. FS is thrombogenic and the evidence for its use in free-flaps is predominantly based on animal models or in targeted pipetting to position the pedicle.(130, 131) There is no evidence supporting its use as a pressurised spray delivery (in keeping with the DEFeND protocol) over microvascular anastomoses in humans. Surgeons are understandably reticent to risk compromise to free tissue transfer, not least because any failures are closely audited both locally and nationally.(132) Given the lack of evidence supporting its use and following discussions with surgeons from Aintree University Hospital (Lead Site) it was apparent that recruitment of these patients was extremely unlikely. Concerns regarding thrombosis at the microvascular anastomosis and ease of re-entering the necks to salvage a free-flap were raised. Since none of the existing research of FS in ND has included free-flap patients, one may argue that this specific use of FS has not progressed far enough along the stages of IDEAL and further early-stage studies are required to assess safety.(127) The counter argument to this approach is to include free-flap patients within the PFS and provide evidence of surgeons' reluctance to recruit, thus informing the definitive trial design. However, the ethics of the latter approach are questionable when there is a dearth of evidence to support safety.

In the post RT/CRT salvage setting surgeons may opt to perform limited NDs that focus on removing isolated malignant lymph nodes without dissection of other levels. Therefore, a judgement needs to be made regarding how to maximise the patient pool while also defining what

constitutes an adequate ND and protecting patients who may be at increased risk of serious adverse events (SAE) secondary to FS.

3.2.3.3 Trial design

The systematic review reported in Chapter 2 revealed that some trials were at high-risk of bias in allocation concealment i.e. the surgeon new the allocation prior to starting the operation.(82) Because FS is an adjunct to wound closure and used at the end of the procedure, the surgeon can theoretically introduce bias and influence the outcome by altering their approach or performance. Also, if the surgeon lacks equipoise, they may decide to withdraw the patient from the trial prior to surgery if the allocation does not suit them. Like DEFeND, the PANasta Trial(133) is a surgical RCT that is in the Liverpool Cancer Trials Unit (LCTU) portfolio. PANasta randomised patients during surgery, however the LCTU had a problematic experience with this process. Randomisation during surgery is dependent on the surgeon accessing software on an NHS computer in an operating theatre. For randomisation to be successful it requires appropriate internet access/bandwidth and security settings that enable access to, and adequate functioning of, the software. Both cannot be guaranteed at specific and time-critical points during surgery, therefore risking the patient not being randomised at all. The DEFeND trial needs to learn from the experiences of PANasta and adopt an alternative approach of revealing the allocation during surgery and immediately before wound closure. This would require novel mechanisms in the trial design and administrative processes to monitor adherence. The evaluation and refinement of these processes prior to a definitive trial are warranted, further supporting the need for a PFS.

Minimising bias in the assessment of outcomes that are subjective (e.g. severity of signs and symptoms) is dependent on an effective blinding strategy. Because the operating surgeon is unblinded, there is uncertainty regarding their influence over blinded patients and outcome assessors. This is especially the case in busy NHS surgical departments where stopping the operating surgeon from reviewing the patient post-operatively is neither realistically governable

nor pragmatic. The operating surgeon may inadvertently and indirectly convey their bias onto patients and outcome assessors. Therefore, a PFS is required to assess the fidelity of the proposed blinding strategy.

3.2.3.4 Outcomes

The choice of primary outcome is a critical decision in trial design. In order that the results of a future IDEAL Stage 3 trial are adopted into clinical practice, the outcome measures need to be meaningful to patients first and foremost. Existing trials looking at FS in ND use outcomes like drain volume, length of drain time and length of hospital stay. Whilst these outcomes impact on patient flow and productivity and are undoubtedly relevant to healthcare providers, their importance to patients is less clearly defined.

There is currently no published core outcome set (COS) for head and neck surgical trials to guide this decision-making process for the DEFeND trial. Some guidance can be gleaned from a 'core information set' for informed consent prior to surgery that has been published using the Delphi technique.(17) Key stakeholders included patients, surgeons and allied health professionals. The final core information set included "details of drips, drains and tubes" and supports unpublished qualitative data from the 'Aintree Head & Neck Patient Research Forum' that demonstrated patients have an aversion to surgical drains as they are uncomfortable and an impediment to mobilisation. 'Time to drain removal' is a very short-term outcome measure and would move the DEFeND trial away from a pragmatic design. The decision to remove a drain is often a clinical decision based on the volume and appearance of the drainage fluid. Surgeons often use various arbitrary volume cut-offs in the decision to remove drains, none of which are particularly evidence based. Using 'time to drain removal' as a primary outcome measure may require standardisation in the protocol to minimise bias and make results comparable between patients. However, in doing so, the trial becomes more explanatory in nature.

Relevant to the DEFeND trial, the 'core information set' also included 'the likelihood of wound problems' and 'details of major or common complications including pain, swelling and bleeding that may require a return to theatre'.(17) Complications after major surgery are a significant cause of morbidity and mortality and have been shown to have a negative impact on long-term quality of life and psychosocial well-being.(134, 135) In surgical oncology, complications can also delay adjuvant RT/CRT which is known to adversely affect survival.(136) Whilst complications after surgery may be a more pragmatic and patient centred outcome, it is not without potential issues. The assessment of complications and their severity is subjective and therefore at risk of bias if the blinding strategy is ineffective. The Clavien-Dindo classification of surgical complications is a well-established tool for assessing the severity of complications, however it is not specific to HNS and therefore open to interpretation.(137) Additionally, because Clavien-Dindo is not specific to HNS, the grade of complication may not be proportional to the morbidity and/or severity of symptoms experienced by the patient. Therefore, guidance on the appropriate grading of complications may be beneficial. Given these uncertainties regarding the use of Clavien-Dindo as a primary outcome measure a PFS may provide valuable insights into its most effective use. Specific issues that may need addressing include uncertainty regarding interobserver variability and how to report the outcome measure. For example, should all complications regardless of severity be reported or only those that reach a prespecified severity? For patients who suffer more than one complication, should the severity of the most serious complication be reported or should the severity of all complications be combined in the form of a summary metric?

3.2.3.5 Trial conduct

The definitive trial will include multiple centres with varying levels of expertise in delivering the intervention and recruiting to surgical trials. The key purpose of a PFS is to ascertain how well the components of the trial work together. An assessment of trial conduct is therefore of fundamental importance. Feedback from research naïve centres regarding difficulties with trial conduct is incredibly valuable to refine the design of a definitive trial. This is because the

components of a pragmatic trial design need to work effectively across varying centres and research environments.

Kaur et al. found that an important key barrier to recruitment to HNS trials was a lack of clinic time to accommodate research.(105) A PFS will enable an assessment of resource use and highlight areas where centres may require further support. Modifying trial design to minimise additional resource use and engaging with the local Clinical Research Network (CRN) are both ways that this barrier may be addressed.

3.2.3.6 Fidelity of the intervention

There is arguably some conflict between a truly pragmatic trial design that allows investigators the freedom to use the intervention as they would in usual practice, and a surgical trial design that wishes to ensure fidelity and standardisation of the intervention. The manufacturers of FS provide instructions that lay out a series of steps on storage, preparation and administration. From the perspective of a surgical trial, it is important that all of these steps are followed.(51, 61) In comparison to learning an entirely novel surgical technique that requires the acquisition of new skills, the use of FS is far less involved. FS does not require the acquisition of new surgical skills but rather an awareness of, and the ability to follow, a set of instructions. The most pragmatic trial design would hand FS to surgeons, allow them to read and interpret the instructions themselves and start using it on trial participants. Whereas a very explanatory trial design would insist participating surgeons have a certain level of expertise and include measures that ensure every step of the intervention is monitored e.g. photographic or video evidence demonstrating compliance. Clearly, if the aim of a definitive trial is to evaluate 'real-world' effectiveness then the pendulum should swing more towards the pragmatic end of the continuum. However, in order to deliver a trial that assesses the intervention in a robust manner, some measures that ensure fidelity and standardisation of the intervention are required.(110) A PFS will provide valuable insights regarding where the balance of flexibility of standardisation should lie in a definitive trial.

Whilst surgical learning curve is of critical importance in the development of novel surgical techniques, its importance in using FS in ND is less clear. Does a surgeon's ability to follow instructions and administer FS improve over time? If so, how should this be evaluated? These are important questions to which the answers are currently unknown. Cook discussed two main options for controlling the impact of learning curve in surgical trials, firstly in the design of the trial and secondly in the analysis.(138) In terms of design, Cook proposes entry criteria for surgeons who have reached a prespecified level of experience or expertise. This approach pushes the pendulum back towards the explanatory end of the continuum and is preferably avoided. In terms of analysis, Cook proposes a post hoc assessment of learning curve that quantifies its effect and adjusts for it in the results. This latter approach is far more in keeping with a pragmatic design however, large numbers of patients are required.(138) Within the context of the DEFeND PFS, comparing surgeons who have differing levels of expertise in using FS is important to understand if learning curve needs to be accounted for in the definitive trial.

3.2.3.7 Sample size calculation for a definitive trial

Whilst a PFS should not be used for formal hypothesis testing, obtaining data that would inform a sample size calculation is legitimate. This is particularly the case when embarking on a pragmatic design when all previous studies have been explanatory. Clearly selection of the most appropriate primary outcome measure is a prerequisite for any calculation. Clinical outcomes from the DEFeND PFS will provide some information on baseline event rates to allow an estimate of effect size. This information will also be critical in deciding whether to proceed with a definitive trial at all in an effort to avoid research waste.(121)

3.3 Rationale for Randomised External Pilot Trial

Based on the uncertainties described in the previous section, we are not currently able to confidently deliver a definitive DEFeND trial and a PFS is certainly justified. According to Eldridge's

‘conceptual framework’ the different types of feasibility studies include feasibility studies that are not pilot studies, non-randomised pilot studies, randomised pilot studies as well as internal pilot studies.(119) Internal pilot studies are studies that form part of a definitive trial in which mechanisms exist to assess the viability of the trial and allow decisions regarding progression. This process avoids research waste by either stopping the trial early or allowing modifications to remediable issues.(139) Given the number of uncertainties about conducting DEFeND and surgical trials more broadly, an internal pilot does not seem an appropriate method. There is a possibility that significant changes to the trial design will be required and therefore a separate study conducted prior to a definitive trial is a more prudent approach.

The NIHR define feasibility studies as those which ask the question “can the trial be done?”(118) Given that there have been many RCTs assessing the role of FS in many different surgical fields, the answer is broadly positive i.e. we know surgical trials assessing FS can be done by virtue of the fact that so many exist. However, if we ask “can a multi-centre trial assessing the role of FS in the field of HNS be done?” the answer is less certain. This is because none of the previous trials assessing FS in HNS have been multi-centre. Many of the uncertainties are related to trial process as well as feasibility of specific design features. On this basis an external pilot study is the best approach. The uncertainty regarding pre-operative randomisation and intra-operative allocation reveal means that a randomised external pilot trial (REPT) is the logical way forward.(119)

‘Feasibility studies that are not pilot studies’ is essentially an umbrella term for all other types of feasibility work.(119) At the time of proposing the DEFeND REPT it was thought that all necessary feasibility work could be conducted as part of the REPT. Reflections of whether this was appropriate or whether some feasibility work should have been done before starting the REPT will be provided in the discussion chapter of this thesis.

3.4 Thesis Objectives

Objective 1: To provide an in-depth narrative of the set-up of DEFeND.

Objective 2: To provide a detailed description of the design of the DEFeND REPT and justify why these features were chosen.

Objective 3: To assess whether the key components of the DEFeND REPT work well together and whether a future definitive trial is feasible.

Objective 4: To explore the different types of outcome measures used in surgical trials and how this may inform the outcome measures used in DEFeND.

Objective 5: To discuss key learning points from the process of delivering the DEFeND REPT and how this would inform future surgical trial design in Head & Neck.

Objective 6: To use the knowledge and understanding gained from DEFeND REPT to decide whether a definitive trial is appropriate and discuss the basis of this decision.

Chapter 4. INSTITUTING THE RANDOMISED EXTERNAL PILOT TRIAL

This chapter will provide a narrative of the PhD candidate's involvement in setting up the DEFeND REPT and interactions with various stakeholders.

4.1 Interaction with the Clinical Trials Unit and Sponsor

The DEFeND Randomised External Pilot Trial (REPT) was funded by the NIHR via the Doctoral Research Fellowship (DRF) stream (project reference DRF-2017-10-117). The study was delivered by the PhD candidate with the support of his supervisory team and through the North West Surgical Trials Centre (NWSTC) and the University of Liverpool (UoL). Interaction with the NWSTC commenced before the funding application process. The NWSTC is one of five Royal College of Surgeons of England surgical trials centres and was established in 2013.(140) At that time, the NWSTC was embedded within the Liverpool Cancer Trials Unit (LCTU). Following a recent merger of the two CTUs based within the UoL, the NWSTC has subsequently been subsumed within the renamed Liverpool Clinical Trials Centre (LCTC).

Early interaction with the NWSTC and LCTU involved negotiating their support for the DRF application and adoption for the study. As the DEFeND REPT design phase was an integral part of the doctoral research training, NWSTC and LCTU similarly agreed to embed the PhD candidate within their structures. This involved providing office space within the unit so that mentorship and support could be provided by senior trial co-ordinators and the operational director. In addition to providing the infrastructure and mentorship to deliver the DEFeND REPT, the NWSTC agreed to provide a practical training in surgical trials methodology and delivery. Following a successful application, the PhD was registered with the UoL and the 3-year DRF commenced in October 2017. Early in the process, the UoL issued a letter confirming their intention to sponsor the study pending approval of all the necessary working documents.

In broad terms the agreed format of the DRF was to setup the study in first year, recruit in the second year and analyse/write up in the third year.

During the DRF the PhD candidate was embedded within the NWSTC and began the process of setting up the trial. This was achieved by the candidate being supervised in the role of Trial Co-ordinator while simultaneously completing the Principal Investigator (PI) role within the lead site (Aintree University Hospital). Before embarking on this project, it was necessary to engage with the MHRA and establish whether they considered FS to be an investigational medicinal product (IMP). The MHRA agreed that FS was **not** an IMP and that DEFeND was therefore **not** a Clinical Trial of an Investigational Medicinal Product (CTIMP). This was important to establish early as it would have significant implications regarding the study's regulatory requirements.

4.2 Overview of the PhD Candidate's Role in Trial Set-up

4.2.1 Protocol development

The pre-trial systematic review Chapter 2 provided valuable insights into what any future trial should look like (Section 2.7). The overall design of the trial underwent a robust review process both in the preparatory and assessment phases of the application. In the preparatory phase advice from the Research Design Service (RDS) was sought and the proposed trial design was heavily critiqued by the candidate's supervisory team (including senior trial coordinators from LCTU and the operational director). The DRF application required a detailed description of the trial design that was peer reviewed and examined in-depth during the selection process.

At the start of the DRF the PhD candidate held meetings with his supervisory team to finalise the trial protocol and construct the working document. Due attention was given to the feedback provided throughout the application process. The Patient Information Sheet (PIS), Informed

Consent Form (ICF) and GP letter were also written by the PhD candidate and approved by patient members of the Aintree Head & Neck Research Forum, ensuring essential patient and public engagement. Copies of these documents can be found in Appendix A. (A.1 Protocol, A.2 Patient Information Sheet, A.3 Informed Consent Form, A.4 GP Letter). An in-depth description of the trial design and rationale behind specific features will be provided in the Chapter 5. and Chapter 6. .

4.2.2 Research Ethics Committee and Health Research Authority approval

Because the proposed study design involved patients that would be identified, randomised and treated within the NHS, ethical approval was a mandatory requirement. The PhD candidate commenced the process of obtaining ethical approval by completing and submitting the Integrated Research Application System (IRAS) form. The process also allowed for the NIHR Clinical Research Network (CRN) application form to be completed simultaneously, an essential component for subsequent portfolio adoption and CRN support for trial delivery. Supporting documentation included the protocol, PIS, ICF, GP letter, CVs of named investigators, a model Research Site Agreement, Statement of Activities and Schedule of Events. The research site agreement, statement of activities and schedule of events is discussed later in section 4.4. The PhD candidate and Primary Supervisor attended the Northwest – Greater Manchester East Research Ethics Committee (REC) application review panel in person. This facilitated provision of direct responses to REC queries and was considered best practice in support of a critical element of research conduct. The following list of changes was requested by the REC (clarification is provided in brackets to add context to some points):

1. Changes to the PIS.

    a. Make it clear throughout that the participants are taking part in the pilot study and not the main clinical trial.

b. Under the heading “Do I have to take part?” please state that it would be of interest to understand the reason for withdrawal however this information does not have to be disclosed.

c. Remove the picture of the Fibrin Sealant.

d. Please specify to Patients that the Fibrin Sealant would be sprayed directly on their wound, the Participant Information Sheet does not give detail to this.

e. Include two additional risks, allergy and fluid collection.

f. Remove the word “only” when stating risks.

g. The heading “What if there is a problem?” should detail the risks involve with taking part not addressing complaints. Please see the HRA website for guidance if needed.

h. Please include a heading regarding the complaint’s procedure, refer to the HRA website for guidance if needed.

i. Participant Information Sheet Part 2 does not detail any points of contact for complaints. Please specify Researcher details and also Research Governance which has already been listed in A4 of the IRAS Form.

j. Remove text regarding Patient samples being sent around Europe, ensuring patients are aware that their samples will eventually be destroyed (samples were taken for a sub-study that the PhD candidate was not involved in and did not influence the DEFeND trial).

2. Within the Informed Consent Form remove the three points in italics (these points referred to a sub-study that the PhD candidate was not involved in and did not influence the DEFeND trial).

3. Please provide script which will be used alongside the power point presentation (this refers to a power point presentation that was produced to assist investigators in explaining the premise of the trial using visual aids, however, this was not considered necessary and was never used).

After these amendments were made, approval from the REC and Health Research Authority (HRA) was granted on 15/05/2018 (reference 18/NW/0209).

Following this approval, the trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) database on the 16/05/2018 (reference ISRCTN99181100). Registration of clinical trials improves research transparency and is important to fulfill the ethical obligations towards trial participants and the research community as a whole. It does this by preventing duplication of research and allowing researchers to access information that may guide healthcare decisions, thereby reducing publication bias and selective reporting. Trial registration is also a requirement for publication in many peer reviewed journals.(141, 142)

There was a need to make a subsequent substantial amendment to the protocol due to the addition of a Patient Reported Outcome Measure (PROM). There were no further changes to the trial protocol following this and the REC and HRA approved the final version of the protocol on 10/09/2018. A substantial amendment is defined as a change to the protocol or other submitted document that affects: the safety or physical or mental integrity of trial subjects; the conduct or management of the trial; the scientific value of the trial; the quality or safety of any IMP used in the trial. (Ref ct-toolkit) The addition of a PROM was thought to constitute a change in the conduct of the trial.

4.2.3 Construction of working documents and university sponsorship

A list of the key working documents the PhD candidate constructed is provided below. They were produced utilizing prior templates created by the LCTU and guidance from senior trials unit staff. Once these working documents were signed off by the Chief Investigator (CI) and

senior LCTU staff, the UoL confirmed sponsorship of the study. Copies of these documents are provided in Appendices A.5 – A.12. The details that are specific to trial design will be discussed further in Chapter 5. .

1. Risk assessment (A.5). Some host organisations will only sponsor trials of a certain risk level. This document seeks to define the overall risk of the trial design and protocol to enable that decision. Risk was assessed on the basis of the intervention, safety of participants, trial results, resources and governance. The DEFeND study was considered to be of low risk overall. Design features such as the use of electronic Case Report Forms (eCRF) and the organisational complexity (being multi-centre surgical trial and including a relatively research naïve site) did mean that specific components were deemed to be of intermediate risk.

2. Internal delegation plan (A.6). The purpose of this document is to identify the trial related processes and activities that will take place within the UoL and document the roles and responsibilities of study personnel.

3. Data management plan (A.7). This aims to ensure that the data are of the highest quality, that there is conformity across trial teams, and demonstrates that there are robust systems to provide quality checks and validation. The PhD candidate and supervising Database Developer took responsibility for all data management tasks. Tasks that were specifically performed by the PhD candidate included eCRF development (see section 4.3), developing data entry guidelines, developing and administrating the data query processes and data quality assurance.

4. Monitoring plan (A.8). Trial monitoring is carried out to ensure the rights and safety of participants are protected as well as ensuring the reported trial data are accurate, complete and verifiable from source documents. The DEFeND trial used central monitoring with triggered monitoring visits. Details of the criteria for monitoring visits is provided

in the document (A.8). Also included are details of central monitoring of recruitment, safety, protocol and regulatory compliance and source data verification.

5. Safety plan (A.9). This document details the process of recording and reporting adverse events. It includes what type and severity of adverse event (AE) should be reported as well as what constitutes an expected and unexpected AE. Once the AE has been reported, the document details what events need to be expedited, how causality is assigned and how the event will be reported to the REC, sponsor and investigators.

6. Randomisation instructions (A.10). This document details the process of randomising patients into the DEFeND trial.

7. Unblinding instructions (A.11). This document details the process of unblinding patients in the event that the allocation needs to be known.

8. Trial Steering Committee (TSC) charter (A.12). This document details the roles and responsibilities of the TSC and its relationship with other oversight committees.

4.2.4 Patient & public involvement

The study design and protocol were developed through collaboration with the Aintree Head & Neck Cancer Patient Research Forum, as consumers and patient advocates. A focus group of five members met to discuss the research question and proposed research project. The group had worked with each other on previous studies and were comfortable sharing their personal experiences of surgery. The group was sent a plain English summary of the research prior to the meeting. The meeting was moderated by the PhD candidate and followed a semi-structured process. The patients were asked open ended questions about their thoughts on the proposed research and could express their views freely. The meeting was not recorded, and anonymity of patients was maintained. The PhD candidate reflected on the meeting and made changes to the trial design according to the issues raised.

4.2.4.1 Research question & trial design

Regarding the overarching aim of this research, to improve the outcomes of patients undergoing ND, the group felt that reducing complications was an important patient centred outcome for a future trial. They also reported that drains in the neck caused considerable discomfort and restricted mobility. They felt that any technique that reduced complications and allowed quicker removal of drains would substantially improve the patient experience.

Regarding trial design, the group raised concerns about the possibility of allergic reactions to FS. Aprotinin, the antifibrinolytic constituent of FS is a bovine protein and known to cause allergic reactions. The incidence of allergic reactions to the Aprotinin component of FS is reported to be 0.5 per 100,000 exposures. Furthermore, allergic reactions are much more frequent in patients who have had previous exposure. To address this patient concern and minimise the risk of allergic reactions, the eligibility criteria were changed to exclude patients who had a known previous exposure to Aprotinin or an allergy to dairy products (as Aprotinin is a bovine protein). The possibility of formal allergy testing of patients with Aprotinin via a skin prick test was explored. The use and funding of additional resources as well as the logistical complexities of obtaining this test result within a suitable timeframe, was thought to create a significant barrier to recruitment. Given Allergic reactions were so rare and would occur in a monitored patient with a secured airway (under general anaesthesia), the balance of risk versus benefit fell on the side of not pursuing this approach.

4.2.4.2 Trial management

The chairman of the Aintree Head & Neck Research Forum offered formal ongoing support for the study and was appointed as the patient representative for the TSC. Having him as a TSC member enabled easy access to the opinions of patients within the research forum.

4.2.4.3 Developing patient information resources

Effective communication with participants is vital to trial success.(143) It stands to reason that being given excessive and complex information regarding the study can be overwhelming for

patients who are due to undergo surgery for cancer. Furthermore, in a survey of 'what makes a study successful' 92% of study personnel thought that a simple consent process was important.(144) The involvement of patient representatives in the construction of participant information resources (i.e. PIS, ICF) is therefore highly valuable. They are able to provide a patient's perspective on the suitability of content, format and language.

Patients from the Aintree Head & Neck Research Forum were provided with drafts of the PIS and ICF and asked to comment on them. By and large they were happy with the content, format and language requesting only minor changes. These documents were then reviewed by the REC who requested the changes specified in section 4.2.2.

4.3 Case Report Form Development

Once the protocol was finalised, work on the Case Report Form (CRF) began. It was decided to implement an electronic CRF (eCRF) as this has several advantages over the more traditional paper CRF. eCRFs are better suited to large multicentre studies due to their ease of administration. Repetitive data (e.g. Participant ID) are generated automatically and data from different pages can be linked. Furthermore, if investigators miss data or enter invalid formats, immediate data alerts are generated to promote efficient resolution. Ultimately this results in better data quality that is available for central review immediately. Paper CRFs prone to data errors and require investigators to upload data, an additional step that may introduce further errors.(145) A potential disadvantage to eCRFs is that they require training to be delivered to sites and continuous IT support. Furthermore, access to the eCRF software via NHS computers can be problematic in trusts with high levels of internet security. This problem was encountered when opening the DEFeND trial at the second site. The NHS trust had to make a special allowance for the software thus increasing bureaucracy and delaying site opening.

Direct entry into the eCRF was not done for the 'Day of Surgery' form which contained operative details. In this instance surgeons completed a paper CRF that was later transcribed into the

eCRF by research staff at site. The reasons for this were essentially pragmatic and logistical, but also critical to maintenance of blinding. Research staff at site were blinded to the allocation and therefore, not allowed in the operating theatre. Relying on surgeons, who may not be familiar with the research process, to access and complete the eCRF may have resulted in missing data that could not be easily completed retrospectively. Within the context of a busy operating list, a surgeon who has forgotten their eCRF login details may not enter any data at all. Furthermore, because surgical trainees rotate through departments regularly, keeping up with the provision of eCRF training and login details adds complexity which threatens the quality of data. Because all surgeons routinely complete operative notes, providing them with a paper CRF to complete at the same time seemed the most reliable and pragmatic approach.

The MACRO Electronic Data Capture System (version 4) produced by Elsevier was used as the eCRF platform.(146) This platform was used because the LCTU had significant expertise. LCTU provided all necessary training for the PhD candidate to design and implement the eCRF within MACRO for the DEFeND REPT. MACRO is compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) standards.

The development of the eCRF was a complex process that was conducted over several stages. Several novel approaches not previously implemented by the LCTU were also incorporated into the design. Once the protocol had been finalised, the first stage in eCRF development was to acknowledge that data needed to be collected for each patient encounter (using the CONSORT diagram and SPIRIT figure presented in the next chapter). These encounters were then classified as ‘Screening’, ‘Baseline’, ‘Day of Surgery’, ‘Inpatient Assessment’, ‘Follow-up 1’, ‘Follow-up Unscheduled’, ‘Follow-up 2’ and ‘Premature Discontinuation’. The ‘Inpatient Assessment’ and ‘Follow-up Unscheduled’ encounters were set to automatically repeat i.e. once data for one episode had been entered another encounter would automatically be generated. This would allow data entry for multiple inpatient days and unscheduled follow-up visits. Having classified each patient encounter within MACRO, the individual data forms were constructed.

In addition to screening and baseline data, each form would correspond to different outcome measures. This would enable individual forms to be attached to each patient encounter. Figure 14 demonstrates an example of the 'Data Management" page. The first row of headings demonstrates each patient encounter, and the first column of headings demonstrates the individual data collection forms. The green ticks signify that the data collection form has been completed satisfactorily for a specific encounter, the blue box icons signify that the data collection form is empty and the sun icon signifies that data has been entered but there is a 'data query' (e.g. missing data field or data error). In this example the patient was randomised, underwent surgery as planned and was discharged on the first post-operative day. They attended all follow-up visits with no unscheduled visits however, data entered in the 'WHQValidation' form was incomplete. The trial monitor can easily review these 'Data Management' pages for each patient currently in the trial and ask sites to make necessary corrections to improve data quality.

Figure 14 Example Data Management page of electronic case report form.

Having established the Data Management page, the next stage in eCRF development was the construction of the individual data collection forms (vertical headings in Figure 14).

4.3.1 Pre-randomisation forms

The pre-randomisation forms included the 'Screening', 'Eligibility Criteria', 'Baseline Data', 'NDII' and 'PainVAS' forms. These forms were required to be completed fully before the software enabled the patient to be randomised. The process of completing these forms prior to randomisation ensured that only patients who had been adequately consented and met the eligibility criteria could be randomised. Using the MACRO eCRF software to prevent the accidental randomisation of ineligible patients was a novel element designed by the PhD candidate and had not been implemented by the LCTU in previous trials.

4.3.1.1 Screening form

The contents of the 'Screening' form are demonstrated in B.1. The form requires investigators to enter some basic patient identification data. The key design feature in the page is that once the investigators click "yes" to the "Trial consent form signed?" question, an automated email is generated to the trial specific email address informing the central trial team that they need to authorise a consent form. The investigators at site were required to upload a scanned copy of the original signed consent form via secure file upload system for the DEFeND trial located within the LCTU online portal.

4.3.1.2 Eligibility criteria form

The contents of the 'Eligibility Criteria' form are demonstrated in B.2. This form takes the investigators step-by-step through the eligibility criteria. If the investigator ticked a response that suggested the patient was ineligible, the eCRF would be locked and no further data could be entered unless the response changed. Once the eligibility criteria had been met, the investigator was required to electronically sign-off their responses using their login details. This electronic signature then generated an automated email to the PI to double check and ratify the

eligibility criteria. Responsibility to ensure only eligible patients were recruited to the study at a particular site was delegated to the PI. Only once this process of checks was complete could the patient be randomised.

4.3.1.3 Baseline data

Baseline data included details on patient demographics recorded in the 'Baseline Data' form (B.3) and pre-operative patient reported outcome measures (PROMS). The preoperative PROMS recorded were the 'Neck Dissection Impairment Index' (NDII) form (B.4) and the 'Neck Pain Scale' form (B.5). Investigators transcribed the patient's responses into the NDII form and the eCRF automatically calculated a raw and standardised NDII score. This was done by writing a computer code that reproduced the calculation.(147) Further details on these PROMS can be found in Chapter 6. .

4.3.2 Randomisation form

The 'Randomisation Form' is a key design feature of the eCRF and can be seen in B.6. This form was automatically populated by the completion of previous forms. Once the consent form was uploaded it was authorised by two independent central trial team members. If satisfactory, they electronically signed-off the consent form. Once two independent checks had been completed the investigators at site could progress through the form. The boxes for 'eligibility criteria signed-off by PI' and baseline PROM data were auto-populated. Once they had all been populated with a positive response, the investigator at site could electronically sign-off the pre-randomisation checklist as complete. Only then could the patient be randomised.

To randomise a patient the investigators accessed the Treatment Allocation RanDomIsation System (TARDIS) software version 3.8 and selected the patient ID to be randomised from a dropdown list of patients who had completed their pre-randomisation checks. As patients were stratified according to site, the investigator was required to select which hospital the patient was being treated in. The patient was then randomised and a message sent from TARDIS

informing MACRO. Importantly the allocation was not visible to the investigators who randomised the patient and was not revealed in MACRO to maintain the blinding strategy. Once the patient was randomised an automated email was sent to the consultant in charge of the patient's care which contained a link to reveal the allocation. This link was only to be selected at the time of wound closure and included relevant warnings to this effect as a step to ensure the allocation was revealed appropriately.

This process was designed by the PhD candidate with assistance from a member of the LCTU Information Systems team. Assistance was required to create effective lines of communication between the software packages and enable automated emails.

4.3.3 Surgery form

As previously mentioned, the Day of Surgery form was a paper CRF that was completed by the surgical team in theatre and later transcribed in the eCRF by the research team. B.7 demonstrates the paper CRF, and B.8 demonstrates the eCRF version. There were two key design features of the eCRF. Firstly, the list of surgeons present in theatre was cross-referenced with clinicians who performed outcome assessments to alert investigators if they were unblinded. Secondly, the start and finish times of surgery were recorded as well as an automatically populated time for when the surgeon revealed the allocation. This alerted investigators if the surgeon revealed the allocation before the start of surgery thereby deviating from the protocol. This feature also allowed investigators to review how far into the surgery the allocation was revealed because FS should be used towards the end of surgery (at the point of wound closure).

4.3.4 Outcome measure forms

The outcome measure forms included the 'Post-Operative Complication Form' (B.9), 'Drain Output Data Form' (B.10), 'Hospital Discharge Form' (B.11), End of Trial Form (B.12), NDII

Form (B.4), Neck Pain Scale Form (B.5), Wound Healing Questionnaire (WHQ) Form (B.13) and the WHQ Validation Form (B.14).

4.3.4.1 Post-operative complication form

Post-operative complications were assessed by surgeons. If the surgeon was not granted access to the eCRF they would be supported by a research practitioner who was conversant with the process. There were two important design features in this form aimed at ensuring outcome fidelity (B.9). Firstly, the name of surgeon making the assessment was recorded and cross-referenced with the names of the surgeons present in theatre. If there was a match, an alert would be generated informing investigators of a data error. Investigators could still override the alert and continue to enter data with the full knowledge that an unblinded individual was assessing outcomes. This would constitute a deviation from the protocol and trigger a root cause analysis to identify why this occurred and how it may be prevented in the future.

Complications were assessed using the the Clavien-Dindo classification to grade severity(23). Within the context of HNS, there are recognised issues with inter-observer variability.(137) To minimise the possibility of this, common complications were listed and a description of what constituted each grade of severity provided (see B.9). It was thought that providing this description would help reduce inter-observer variability. For rare complications an 'Other Complications' question was included, however, this required investigators to make their own assessment of the most appropriate grade of complication.

4.3.4.2 Drain output data form

The Drain Output Data form was perhaps the most complex form as it needed to implement the standardised protocol for drain removal (demonstrated in B.10). At the start of the study design process, it was believed that the criteria for drain removal needed to be standardised because the secondary outcomes 'drain volume' and 'time to drain removal' were considered integral to the research question. Surgeons may use different criteria to remove a drain and a non-standardised approach would produce heterogenous data (depending on how many

patients were recruited by each surgeon). This may allow detection bias to creep into the study design. For example, a surgeon present in theatre who reviews the patient post-operatively may influence the clinical outcome by recommending when the drain should be removed. A standardised approach adopts a drain protocol that takes the decision away from clinicians. However, in hindsight this also made the trial design less pragmatic.

The drain protocol/algorithm was developed by the PhD candidate and summarised in Figure 15. The reasoning behind this algorithm is discussed in detail in section 6.2.1.2. Essentially the drainage volume was measured at two different time points within a twenty-four-hour period (morning and evening). Given the busy nature of surgical wards it was felt important not to have a specified time for drain measurement as this may result in frequent protocol deviations. Instead, the time for drain measurement was flexible and focus placed on the rate of drainage rather than the volume at a specified time. The rate of drainage was automatically calculated by the eCRF once the investigators entered two time points between which the volume was measured. After surgery the patient would have their drain measured and emptied that same evening. The time and volume of this measurement would be recorded in the fluid balance chart of the patient's medical records. The following morning the drain would be measured again by research staff with access to MACRO. They would record the time and volume measured in the morning as well as the time of measurement the previous evening. This would provide the eCRF with two time points and volume with which to calculate a rate of drainage. The flow diagram in Figure 15 demonstrates the algorithm that was programmed into MACRO by the PhD candidate. If the rate of drainage was less than 1.25ml/hr the eCRF would inform research staff to remove the drain. If the rate was greater than 2.09ml/hr research staff were informed to leave the drain in situ and re-measure in the evening. Importantly, in keeping with safe surgical practice, no drains were removed in the evening. This practice stems from the fact that the act of drain removal may on rare occasions result in bleeding and therefore is not performed at night when there are fewer nursing and surgical staff on site. Furthermore, patients tend not to be discharged home late at night and therefore immediate drain removal at this time would be unlikely to derive benefit (such as reduced length of stay). If the rate of

drainage fell between 1.25ml/hr and 2.09ml/hr, research staff were instructed to re-measure in the afternoon. This was because this intermediate rate may signify a slowing of drainage and, if re-measured in the afternoon, may result in safe removal of the drain whilst also providing an opportunity to discharge the patient from hospital that day.

DEFeND Drain Measurement and Removal Protocol

The protocol is based on the widely used cut-off of less than 30ml in 24 hours for drain removal.

Drain output should be measured at a minimum of 2 time points during the day (morning and evening). The contents of the drain are emptied into a measuring cylinder for every reading.

Because these time points may vary slightly from day to day we are interested in the rate of drain output as well as the volume.

The MACRO database will automatically calculate the rate for you. The flow chart describes the decision making process in more detail.

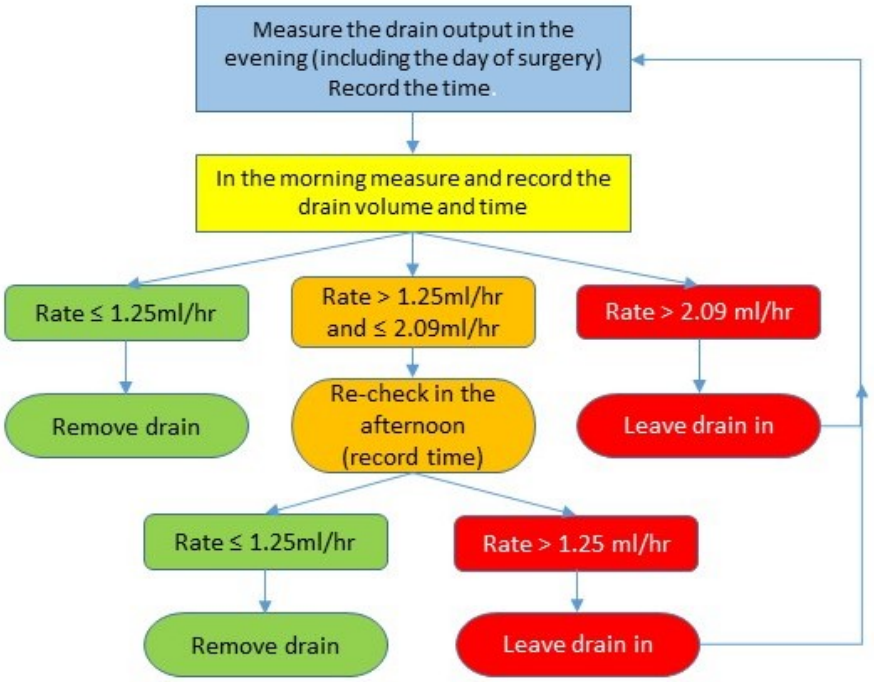


Figure 15 Drain removal algorithm

The research staff were required to enter the exact time and date of drain removal as this may have been different to the time of drain measurement. The eCRF was programmed to add all the drain volumes together to provide a total volume drained as well as a daily volume.

4.3.4.3 Hospital discharge form

The Hospital Discharge Form shown in B.11 recorded the time and date of hospital discharge. The name of the outcome assessor making the decision to discharge the patient was cross-referenced with the list of surgeons present in theatre. If there was a match, the eCRF would alert the research staff that the outcome assessor was unblinded and deviating from the protocol. This would enable the research staff to ask another clinician to assess whether the patient was suitable for discharge. If an unblinded outcome assessor was allowed to make the decision to discharge, the trial monitor would be aware of the deviation and would need to instigate a root cause analysis.

4.3.4.4 End of trial form

The End of Trial Form shown in B.12 was a relatively simple design that required direct responses to the questions and was not linked to any other forms. In order to assess the fidelity of the blinding process the patient, research nurse and blinded surgeon were asked whether they thought the patient received the intervention or not. They graded the confidence of their response using a 5-point Likert scale that was used to assess the fidelity of the blinding process (5.8)

Research staff were also requested to record the number of lymph nodes harvested within the neck dissection. This information was derived from the final pathology report and used as a quality assurance indicator to monitor whether patients were undergoing adequate dissections.(148) The final box on the form was a free-text box where research staff transcribed the patient's response to a question regarding the minimal clinically important difference (MCID). The reasoning behind the question is discussed further in section 5.12.4.

4.3.4.5 Patient reported outcome measure (PROM) forms

The PROM forms include the 'NDII Form' (B.4), the Neck Pain Scale Form (B.5) and the Wound Healing Questionnaire (WHQ) form (B.13). The rationale behind selecting these PROMs is provided in section 6.2.2. These forms simply reflected details provided in their relevant publications.(147, 149, 150) The NDII and Neck Pain Scale were recorded at baseline as well as at the final visit. The WHQ form was recorded at the final visit only. The questions were delivered to patients either by printing off the eCRF form and asking patients to complete the questions independently or by research staff reading out the questions to the patient. The WHQ was developed by researchers at the University of Bristol and is not validated for use in HNS patients.(149) Permission to use the WHQ was obtained through collaboration. They requested that the WHQ Validation questionnaire (B.14) was completed by surgeons assessing the patient at the final visit. Anonymised data from the WHQ and WHQ Validation forms was sent to them in the form of a spreadsheet on a monthly basis.

4.3.4.6 Electronic case report form completion guidelines

Research staff at site were trained to use MACRO during the process of site opening. The PhD candidate instructed them on how to login, create a new patient and enter data. Once their training was complete the LCTU provided them with their own personal login details. In addition to this initial training research staff were provided with the eCRF completion guidelines (B.15) as part of the investigator site file. Furthermore, the PhD candidate, in the role of Trial Monitor and Trial Co-ordinator, was easily accessible to troubleshoot and assist research staff at site to ensure data quality. B.16 shows the working document for the Data Query process. This is the process by which site staff can enter queries and communicate with the Data Monitor (PhD candidate) through the MACRO platform. However, this process was often bypassed by research staff who preferred to liaise directly with the Data Monitor (PhD Candidate).

Before the eCRF was made 'live' for use on trial participants, the PhD candidate and IT department practiced data entry with artificial patients and scenarios. Once both parties were satisfied

that the eCRF was fit for purpose, the IT department then undertook its routine authorisations as part of the 'Green Light Process' (see section 4.4.2).

4.4 Site Initiation and Green Light Process

The DEFeND trial recruited patients from two sites, Aintree University Hospital (Lead Site) and Queen Victoria Hospital (QVH). Aintree University Hospital (AUH) was chosen because it is one of the busiest HNC centres in the UK and a leading centre for HNC research. Furthermore, both the PhD candidate and Chief Investigator (CI; Schache) are based within the trust (PhD candidate is a trainee and Schache is an Honorary Consultant Head & Neck Surgeon). Both the PhD candidate and CI have close links with QVH, having worked there as higher surgical trainees. Furthermore, following the recent appointment of an academic Head & Neck Surgeon, QVH had expressed an interest in expanding their clinical trials portfolio. Prior to their involvement in DEFeND, QVH had a very limited experience of delivering surgical trials. At the time their lack of experience was considered beneficial to assessing the pilot and feasibility outcomes of the trial. QVH is a non-academic centre which is representative of many HNC services in the UK. Therefore, insights gained from their performance in delivering the study was thought to be valuable for improving the design of a definitive trial.

During the set-up phase, subsequent to REC and HRA approval was granted, both sites were required to confirm their capacity and capability to deliver the study. These decisions were primarily made by the respective Research & Development (R&D) departments and based upon the protocol, research site agreement, statement of activities and schedule of events. The research site agreement is a contract between the sponsor (UoL) and the research site. A model agreement taken from the IRAS website(151) was used. In keeping with HRA recommendations this model agreement was unmodified. The Statement of Activities provides the research site with clarity on what funding the sponsor will provide for research costs and better understand the overall cost of the study. The Schedule of Events provides the research site with all the 'per-participant' activities and classifies the funding of them as either NHS treatment

cost, NHS support cost or research cost. NHS treatment costs are the patient care costs that would continue to be incurred if the service continued to be provided after the study had stopped e.g. the cost of performing a ND. NHS support costs are the additional patient care costs associated with the study which would end once the study has finished e.g. the time taken to consent the patient for the study. The research cost is the cost of the study itself and related to activities undertaken to answer the research question. Research costs would end when the study ends.(152)

The funder (NIHR) is a member of the Association of Medical Research Charities (AMRC) and certain activities were undertaken by staff employed by the NHS or NIHR Clinical Research Network (CRN). Under these circumstances the research activities are further classified as either 'Part A' or 'Part B'. The cost of 'Part A' activities are paid in full by the funder whereas the cost of 'Part B' activities are paid by the Department of Health. 'Part A' activities include screening, assessment of eligibility, randomisation, study specific investigations, follow-up appointments in addition to standard care. 'Part B' activities include local study co-ordination, data collection and time taken by the PI/CI to explain the study to professional colleagues.(152)

4.4.1 Site initiation visits

The site initiation visits for both the lead and second site were conducted by the PhD candidate. The purpose of the visits was to ensure the sites understood the protocol in detail and had an opportunity to raise any questions or concerns. The PhD candidate attended both sites in person and gave presentations summarising the trial protocol and important trial related processes. An entire day was set aside for each visit. Topics covered included screening, recruitment, informed consent, randomisation, PI obligations, GCP, contents of the investigator site file, delegation logs, data protection, eCRF completion, safety reporting, monitoring, patient withdrawals and close out. In addition to the presentations the PhD candidate also delivered individual training for research staff on maintaining the screening log, uploading consent forms, eCRF completion, randomisation and safety reporting. Having taken an integral role in

designing the study and completing all the regulatory processes, the PhD candidate was well positioned to answer questions as well as address potential barriers (e.g. communicating with the second site's IT department to authorise access to the eCRF software on NHS computers).

4.4.2 Green light process

The Green Light Process is essentially a process of bringing together all the regulatory and administrative approvals and documents that are required to open the trial to recruitment. A checklist was completed and signed-off by both the Operational Director of the LCTU and the CI. The following requirements needed to be met before the Green Light Process was complete:

1. The sponsor (UoL) had given the green light following REC/HRA approval and the authorisation of working documents described in section 4.2.1, 4.2.2 and 4.2.3.

2. The LCTU IT department had tested and authorised the randomisation process and eCRF for use on trial participants.

3. The research sites had confirmed their capacity and capability as well as undergone their site initiation visits.

4. Clinical Co-ordinators had been assigned and tested in their ability to assess adverse events appropriately and in a timely fashion. This involved them reading the Safety Plan (A.9) and undertaking a test case of a fictional patient. In the test case they were required to read the adverse event report (Located in Appendix 1 of the Safety Plan in A.9), access the LCTU Pharmacovigilance database and assign severity, expectedness and causality. This needed to be performed correctly and within the predetermined timeframe for the Clinical Co-ordinator to be deemed competent.

5. First TSC had been convened to review the trial protocol and to agree upon how future meetings will operate.

Following the completion of the Green Light Process AUH recruited and randomised the first patient on 8th November 2018. With both the PhD candidate and CI supporting surgeons and research practitioners to recruit patients, AUH was able to recruit quickly and effectively. QVH however did not randomise their first patient until 4th February 2019. This was mainly due to their very cautious R&D department that was inexperienced in opening clinical trials. Areas where they differed from AUH included taking longer to read and sign the research site agreement. It became apparent that they wished to minimise the time between opening the site and recruiting the first patient, so it appeared that there was a deliberate delay to site opening until a suitable first patient had been identified. Another concern they raised included limited research practitioner support and their ability to recruit patients and complete the eCRF in a timely fashion. Making contingency plans to cover all the research activity added to the delay in site opening.

QVH follows a slightly different model of HNC services compared to AUH. The catchment area for QVH is a vast area in the Southeast of England which encompasses several NHS trusts and Head & Neck Multidisciplinary Team (MDT) meetings. Patients are managed in outpatient clinics locally (spoke) but operated on centrally at QVH (hub). Concerns were raised by QVH regarding whether patients could be approached and consented at the 'spoke' sites before they attended QVH. This was a legitimate concern however, with site opening already delayed by four months and recruitment limited to twelve months, opening the spoke sites was considered untenable. A decision was made to not open spoke sites and for the PI and research practitioners were asked to work around this issue. A discussion around this decision and its implications on the results of the DEFeND REPT is provided in section 8.1.2.

A detailed description of the trial design and rationale behind the choices made is provided in Chapter 5. The rationale behind the clinical outcome measures that were chosen to inform a future definitive trial is provided in Chapter 6.

Chapter 5. TRIAL DESIGN

5.1 Overview

The study design design being piloted is that of a two arm, parallel group trial with block randomisation in a 1:1 allocation ratio. The interventional arm constitutes the application of FS to the surgical wound in addition to SoC the control arm constitutes SoC alone. For the purposes of this study SoC constitutes the surgeon performing the ND as they normally would and establishing complete haemostasis. Patients in both arms had a single surgical drain placed and the wound closed with resorbable sutures across the platysma layer and metal clips to close the skin. The use of FS or any other adjunct to haemostasis in ND is not commonplace within the UK. For this reason, the selection of SoC as the comparator is justified.

Data was collected and entered directly into the eCRFs by research staff at sites located within the trial's electronic database (MACRO version 4). Delegated staff were given training and access to the software and were expected to input data directly into the eCRF in real time. Each delegated person had a unique username and password to identify who entered the data for audit purposes. Details of the various forms that made up the eCRF have been previously reported in section 4.3 and each forms is shown in Appendix B.

The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Figure 16. The protocol was prepared in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The working document can be seen in Appendix A.1 and the published version can be accessed at: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-020-00618-w. In keeping with best practice, the protocol was submitted for publication in the journal "Pilot & Feasibility Studies" while recruitment was still ongoing.(153) The "SPIRIT 2013 Checklist: Recommended items to address in a clinical trial

protocol and related documents" can be found in the supplementary information associated with the published protocol. The SPIRIT Figure shows the different data collection steps of the pilot trial (Table 8).

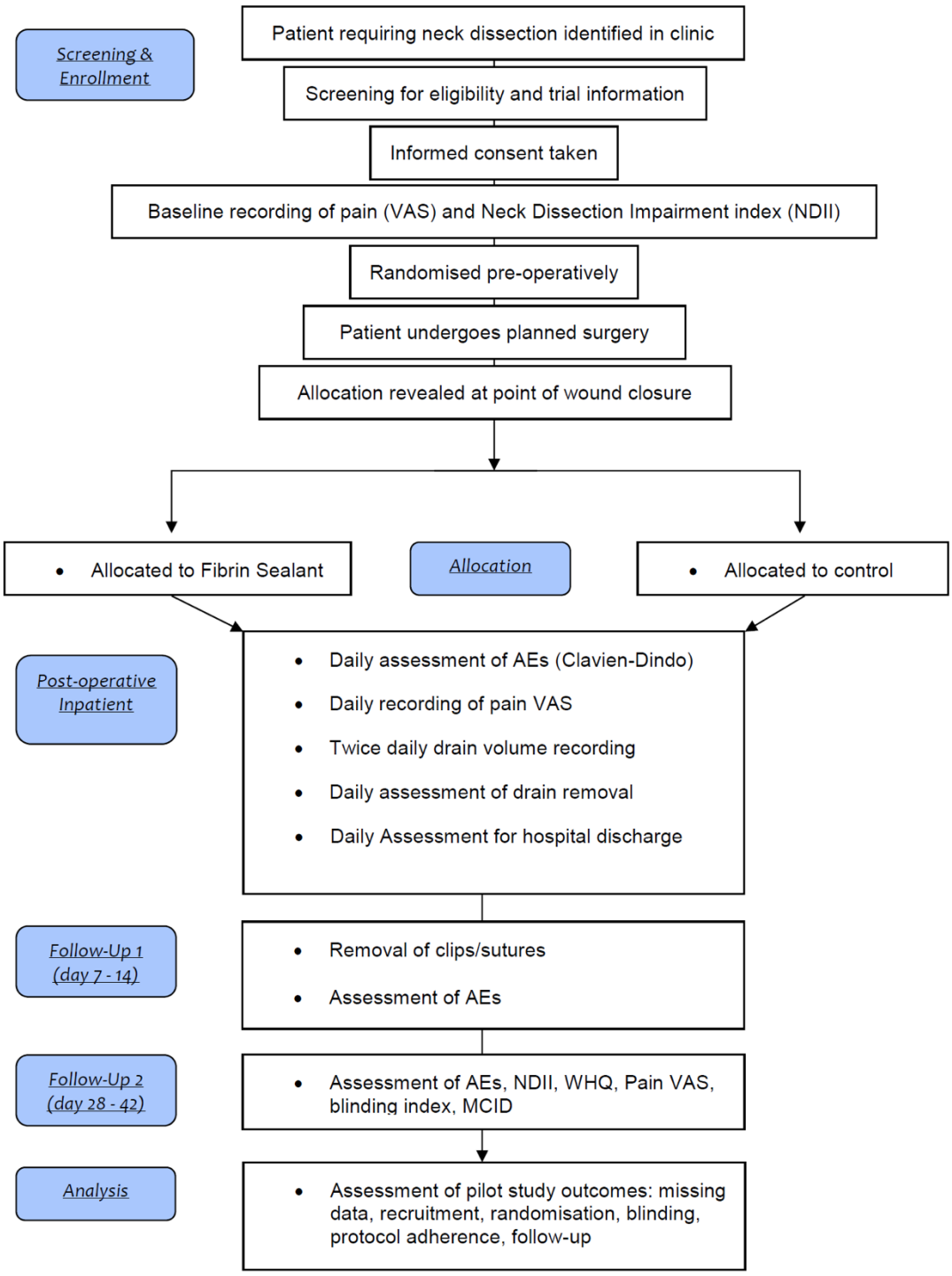


Figure 16 Study flow diagram (CONSORT diagram).

Table 8 SPIRIT figure

Procedures		Head & Neck Clinic/MDT	Screening	Pre-operative Assessment	Baseline*	Day of Surgery (Day 0)	Follow-Up Schedule: Daily In-patient Assessment	Follow-Up Schedule: Follow-up 1 (Day 7 – 14)	Follow-Up Schedule: Follow-up Unscheduled	Follow-Up Schedule: Follow-up 2 (Day 28 – 42)	Premature Discontinuation
Identify potential participant		X	X								
Approach potential participant to discuss study		X	X								
Medical history			X								
Physical examination			X								
Assessment of eligibility criteria			X								
Review of concomitant anticoagulant medications			X	X	X	X	X	X	X	X	X
Review of previous treatment to ipsilateral neck			X								
Demographic assessment			X								
Signed consent form					X						
Randomisation					X						
Assessment of patient reported outcome measures	Neck pain (VAS)				X		X	X	X	X	X
	Neck Dissection Impairment Index (NDII)				X					X	X
	Wound Healing Questionnaire (WHQ)									X	X
Surgical Protocol	Neck dissection surgery					X					
	Allocation revealed at point of wound closure					X					
	Prepare and administer ARTISS (interventional arm only)					X					
Assessment of Clinical Outcome Measures	Assessment of AEs (Clavien-Dindo)					X	X	X	X	X	X
	Wound Drainage Volume (ml)						X				
	Wound Drain Removal						X				

Procedures		Head & Neck Clinic/MDT	Screening	Pre-operative Assessment	Baseline*	Day of Surgery (Day 0)	Follow-Up Schedule: Daily In-patient Assessment	Follow-up 1 (Day 7 – 14)	Follow-up Un-scheduled	Follow-up 2 (Day 28 – 42)	Premature Dis-continuation
	Hospital Discharge						X				
Assessment of Pi-lot Study Out-comes	Assessment of Blinding Strategy									X	X
	Assessment of Minimal Clinically Important Differ-ence									X	X
Laboratory Tests	Full Blood Count**				X						
	PT & APTT				X						
	Pregnancy test (women of childbearing age)				X						
	Histological Lymph Node Yield									X	

5.2 Trial Registration & Governance

The DEFeND REPT was prospectively registered with the ISRCTN registry. ISRCTN99181100 was assigned on 16 May 2018. DEFeND was also registered on the UK CRN study portfolio (Protocol Number: 37896). The University of Liverpool was the sole sponsor for this study (sponsor@liverpool.ac.uk) and had responsibility for trial oversight, indemnity, monitoring trial conduct and governance. All items from the World Health Organization Trial Registration Data Set can be found at: https://doi.org/10.1186/ISRCTN99181100. The study was funded through the NIHR Doctoral Research Fellowship programme (project reference DRF-2017-10-117). The funder and sponsor had no role in study design, data collection, trial management, analysis of results or dissemination.

Research ethics approval was granted by Northwest – Greater Manchester East Research Ethics Committee (REC), reference 18/NW/0209, on 14/05/2018 and subsequently by the

Health Research Authority on 15/05/2018. Written informed consent was obtained from all participants in accordance with this approval. One substantial amendment to the protocol was made and approved on 10/09/2018 which was prior to recruitment of the first participant. The REC agreed that an Independent Data Monitoring and Safety Committee was unnecessary. A Trial Management Group monitored progress approximately monthly. The Trial Steering Committee (TSC) was convened at the start, mid-point and end of recruitment.

5.3 Pilot & Feasibility Objectives

The specific pilot and feasibility objectives for DEFeND REPT are listed below and discussed in more detail in section 5.12.

1. Proportion of eligible patients randomised to the study
2. Reasons for failure to screen potentially eligible patients
3. Recruitment rate
4. Reasons for failure to randomise
5. Number of patients lost to follow-up
6. Reasons for loss to follow-up
7. Reasons for failure to reveal allocation at a specific time point during surgery
8. Fidelity of the blinding process (both patients and outcome assessors) as detected by blinding indices.
9. Accuracy of data recording summarised by the number of key data items with missing or incomplete data entries.
10. Protocol adherence measured by the number of major or minor protocol deviations observed through the study.
11. Determining the minimal clinically important difference (MCID) through semi-structured interviews of trial participants.
12. The relevance of learning curve in a definitive trial

5.4 Setting

The minimum requirements for sites to participate in this study as stipulated in the protocol (A.1) were as follows:

1. **Sites will either have or be part of a comprehensive Head & Neck Multidisciplinary Team (MDT)**. This requirement is based on the national requirement to discuss all patients with HNC in an MDT. Therefore, identifying patients who have been discussed in an MDT was thought to be the most pragmatic design option.
2. **Have surgical expertise in the management of HNC**. This was clearly important because sites are required to perform ND as part of the treatment for HNC. Most HNS services in the UK are centralised and therefore offer a level of expertise. In keeping with a pragmatic design, no minimum level of expertise was stipulated.
3. **Have sufficient caseload to recruit 2 patients per month**. This was based on two sites recruiting fifty patients over a twelve-month period.
4. **Demonstrate enthusiasm to participate in the study**. In order to optimise the chances of success in recruiting to the study and adhering to the protocol a demonstration of enthusiasm is important. From a REPT perspective, the amount of information gleaned from a site will be extremely limited if they fail to drive the study forward.
5. **Provide information to all supporting staff members involved in the trial or other aspects of the patient's management**. Clearly everybody involved in the patient's journey needs to understand that they are part of a trail and the implications this has on their care.
6. **Acknowledge and agree to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to GCP**. This is a mandatory requirement for any research study.

This study was set within two UK hospitals offering tertiary HNS services (Aintree University Hospital NHS Foundation Trust & Queen Victoria Hospital NHS Foundation Trust). The decision to select two centres was considered important because a future definitive trial with a pragmatic design would need to be multi-centre. Both institutions met the minimum requirement for participation and service a large population with a mix of both urban, suburban and rural communities. Aintree University Hospital (AUH) was the lead site and has a strong research portfolio in HNC research. Four of the academic surgeons have experience as Chief Investigators (CI) and a dedicated team of HNC Research Nurses (RN) are on hand to optimise recruitment and trial conduct. Queen Victoria Hospital (QVH) is representative of most non-academic centres across the UK. It has fewer RNs and considerably less experience in delivering RCTs. Understanding the experiences of QVH in delivering DEFeND REPT will be key to the design of the future definitive trial. As previously mentioned in section 4.4, the decision to select QVH as a second site over other possible sites was based on the PhD candidate and CI's having close links. Because QVH expressed an interest in taking part in the study, there was a basis for a constructive working relationship on the study.

5.5 Eligibility Criteria

Every effort was made to keep eligibility criteria as broad as possible such that, in keeping with a pragmatic trial design, the participants in the trial were representative of those who would receive FS if it was part of usual care. The rationale for each of the eligibility criteria is discussed in detail in this section. The criteria evolved through the trial design and set-up process. They were initially drafted by the Trial Management Group (TMG; PhD candidate and supervisory team) and revised by patients from the Aintree Head & Neck Research Forum. They were also evaluated through the process of DRF peer review and REC approval. Finally, they were agreed by the TSC in their first meeting, before the first participant was recruited.

5.5.1 Inclusion criteria

5.5.1.1 Patients due to undergo lateral neck dissection

The rationale for including patients due to undergo lateral ND has already been discussed. The systematic review reported in Chapter 2 concluded that there was a paucity of randomised data with regards to the use of FS in lateral ND. To date there are only two RCTs that have assessed the role of FS in lateral ND (as opposed to central ND).(94, 95) These trials have randomised a total of 75 patients between them. Both trials were more on the explanatory end of the continuum and raise doubts regarding the external validity of their findings.

5.5.1.2 Neck dissection to include a minimum of three levels

As previously discussed in section 1.4, the potential benefits of FS include haemostasis and tissue adhesion to reduce surgical dead-space. Also discussed in section 1.5.1 were the potential benefits of tissue adhesion using low-thrombin concentration FS in lymphadenectomy procedures. It stands to reason that a smaller wound, with less volume of surgical dead-space, has the potential to heal more quickly and with less complications than a larger wound. During the early stages of trial design, the TMG felt that it was important to establish a definition for what constituted the minimum extent of ND. As stated in section 1.2, ND is a surgical procedure that involves removal of lymph nodes (lymphadenectomy) and surrounding tissues from within the neck. There is no widely recognised minimum criteria for what defines a ND. However, there is evidence that a minimum of eighteen nodes harvested results in better survival outcomes and should therefore be used as a quality performance indicator.(148, 154, 155) The 2016 UK Multidisciplinary Recommendations published by the British Association of Head & Neck Oncologists (BAHNO) state that ND for most mucosal, cutaneous and salivary malignancies (whether elective or therapeutic) should involve at least three levels.(156-160) These recommendations are advisory and in an individual case it may not always be appropriate to perform a three-level ND. For example, in the salvage setting when a patient suffers a neck recurrence having already undergone a ND, it may not be possible to harvest eighteen nodes nor

may they be suitable to undertake a three-level ND. In these cases, surgeons often carry out very limited dissections.

Based on the afore mentioned BAHNO recommendations, the TMG took the decision to include patients who had a minimum of three levels dissected. There was an intention to use the clinical outcomes of this small REPT in conjunction with the systematic review (Chapter 2) to justify a definitive trial and the TMG wished to exclude patients who had excisional lymph node biopsies (e.g. sentinel lymph node biopsy). This was because the surgical wounds associated with these biopsies have smaller incisions and less dead space. It was argued that these patients represented a very different cohort to those undergoing a full ND that were not included in the systematic review. Therefore, the potential benefits of FS in this cohort should be assessed outside the DEFeND trial.

Whilst the criteria for a minimum of three levels dissected was in keeping with a national recommendation, it did narrow the eligibility criteria and nudge the trial design towards the explanatory end of the continuum. In hindsight, the extent of ND could have been used as a variable for stratified randomisation and undergoing lymph node biopsies could have been made an exclusion criterion. Excluding patients who had a ND with less than three levels meant an opportunity to fully assess the PFS objectives and inform a definitive pragmatic trial design may have been underutilised.

5.5.1.3 Patients who have capacity to consent

The following paragraphs have been taken from the General Medical Council (GMC) guidance on 'consent to research'.(161)

"Seeking consent is fundamental in research involving people. Participants' consent is legally valid and professionally acceptable only if they have the capacity to decide whether to take part in the research, have been properly informed, and have agreed to participate without pressure or coercion."

"You must only undertake research involving an adult who lacks capacity if it is related to their incapacity or its treatment. You must not involve in research adults who lack capacity if the same or similar research could be undertaken by involving only people with capacity."

Clearly this research is not related to incapacity or its treatment. Therefore, patients were required to have capacity in order to give their informed consent to participate in this study.

5.5.2 Exclusion criteria

5.5.2.1 Under eighteen years of age

In their document '0-18 years: guidance for all doctors'(162), The GMC states that:

"Children or young people should be involved in research only when research on adults cannot provide the same benefits. They can be involved in research that has either:

a. *potential benefits for children or young people generally, as long as the research does not go against their best interests or involves only minimal or low risk of harm (this would be research that involves, for example, asking questions or taking blood samples, the assessment of the risk depending on the view of the child or young person), or*

b. *potential therapeutic benefits for them that outweigh any foreseeable risks, which should be kept as low as possible."*

The SmPC states that ARTISS FS has been used on patients between the age of 1.1 – 18 years safely within the context of a clinical trial.(51) Nevertheless the DEFeND trial does not specifically require children or young people to be involved. Therefore, excluding them would be in keeping with GMC guidance.

5.5.2.2 Bilateral neck dissection

During the design phase, the TMG took the decision to exclude patients undergoing bilateral ND. This was due to perceived logistical problems that may be created by patients undergoing

bilateral procedures. For example, would the clinical outcomes for bilateral ND be recorded individually for each side or as one large wound? If we considered each side individually, should they be randomised separately? Bilateral NDs are in essence two ND wounds in continuity creating a single large wound. Whilst this type of wound normally requires a minimum of two surgical drains (one for each side of the neck), it may not have been possible to consider them entirely independent wounds in terms of drainage. Theoretically, once one drain was removed, a proportion of the remaining drain's volume may have been derived from the contralateral wound. This would be more or less likely depending on the orientation of the drain inside the wound. The uncertainty regarding whether a bilateral ND should be considered one wound, or two individual wounds was managed by excluding them all together.

The 'Drain Output Data' form described in section 4.3.4.2 required investigators to input the drainage volumes between two time points to calculate the rate of drainage. This calculation then informed investigators whether the drain should be removed, re-measured in the afternoon or kept in situ. Creating a similar eCRF that could accommodate multiple drains would have increased complexity and the likelihood of errors. For example, investigators may have easily mistaken the volumes between drains when transcribing the data into the eCRF leading to the wrong drain being removed. Given these perceived logistical issues the eCRF was not designed to record multiple drain volumes, therefore precluding bilateral NDs. Furthermore, the TMG took the view that the number of bilateral NDs performed in patients who did not require a vascular pedicle (to reconstruct the index tumour defect) would be incredibly small and would not impact on recruitment.

Whilst the exclusion of bilateral NDs may not have impacted recruitment, the approach to this issue moved the trial towards a very explanatory design (similar to the excluding NDs less than three levels). In hindsight the perceived logistical issues were self-inflicted by the PhD candidate and, with greater insight into what constituted a pragmatic trial design, may have been easily surmounted. The algorithm used in 'Drain Output Data' form created by the PhD

candidate was ultimately a very explanatory design feature. A more pragmatic approach would have been to not collect drain volume data at all and allow blinded surgeons to remove drains as they would in usual care. As will become apparent from the results of this study, patients are more concerned with early discharge from hospital than the volume of fluid in their drain. 'Time to hospital discharge' was therefore a more patient centered and pragmatic outcome measure. The impact of individual surgeons using a different number of drains or different criteria for drain removal could have been managed either by using stratified randomisation, or simply randomising sufficient numbers of patients to dilute the overall effect. If opting to use stratified randomisation, preliminary surveys of surgeons' drain practices would have been required to establish the stratification variables.

5.5.2.3 Presence of a vascular pedicle for reconstruction

The decision to exclude patients whose ND wounds contained a vascular pedicle for reconstruction was made by the TMG early in the design phase and has previously been discussed in section 3.2.3.2. There was a lack of evidence regarding the safety of using FS delivered through a pressurised spray over microvascular anastomoses in humans. One may argue that this specific use of FS has not progressed far enough along the stages of IDEAL and further early-stage studies are required to assess its safety.(127) Therefore, the ethics of including these patients was questionable. If a future definitive trial is performed, the TMG should be open to the possibility that future research may provide evidence of safety and be willing to make amendments to the protocol that allows inclusion of this cohort of patients.

5.5.2.4 Pregnancy or breast feeding

The SmPC for ARTISS (51) states the following:

- *"The measures taken (to prevent transmission of infection) may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection)…"*

- *"The safety of fibrin sealants/haemostatics for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Animal studies have also not been performed. Therefore, the product should be administered to pregnant and lactating women only if clearly needed."*

Based on this information patients who were pregnant or breast feeding were excluded from the trial. Females of childbearing age were offered a voluntary pregnancy test as part of the study if they wished to participate. The Eligibility form shown in B.2 demonstrates how eligibility for females of childbearing age was determined. In the event that the patient became pregnant after recruitment to the trial, there was a requirement to complete a 'Pregnancy' form that would be reported in the same way as Serious Adverse Event (SAE). Details of this process can be found in section 6 and Appendix 6 of the Safety Plan demonstrated in A.9 of this thesis.

5.5.2.5 Increased risk of allergic reaction

The relevant section of the SmPC(51) states the following:

- *"ARTISS contains aprotinin. Even in case of strict local application, there is a risk of anaphylactic reaction linked to the presence of aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore, any use of aprotinin or aprotinin containing products should be recorded in the patients' records."*
- *"As synthetic aprotinin is structurally identical to bovine aprotinin the use of ARTISS in patients with allergies to bovine proteins should be carefully evaluated."*

As already mentioned in section 1.4.3, Aprotinin is an antifibrinolytic agent that prevents premature proteolytic degradation of the FS polymer. The statements from the SmPC quoted above clearly recognise Aprotinin hypersensitivity as a risk to patients. Representatives from the Aintree Head & Neck Research Forum (as discussed in section 4.2.4.1) requested that measures to reduce the risk of allergic reactions be undertaken. The possibility of formal skin prick testing was explored but, due to requirements to access third party resources, were found to be

prohibitively complex and a potential barrier to recruitment. Therefore, to ensure the concerns of patient representatives were adequately met, the eligibility criteria were adjusted to minimise the risk of allergic reactions. Eligibility criteria defined an 'increased risk of allergic reaction' as follows:

- **Known hypersensitivity reaction to Aprotinin**. As would be expected, patients with a known hypersensitivity reaction to Aprotinin were excluded from the trial.

- **Previous exposure to FS within the last six months**. As stated in the SmPC, there is an increased risk of Aprotinin hypersensitivity if the patient has been previously exposed. In an analysis of over 12,000 Aprotinin exposures, Dietrich et al found that the risk of Aprotinin hypersensitivity decreased with time.(163) The study of cardiac surgery patients found the rate of hypersensitivity after previous exposure to Aprotinin to be 4.1% within six months, 1.9% between six to twelve months and 0.4% after twelve months. Based on this study an exposure after six months was considered an acceptable risk by the Aintree Head & Neck Research Forum and TSC.

- **Known allergy to dairy products**. As stated in the SmPC patients with allergies to bovine proteins should be "carefully evaluated". Based on this statement a decision was taken to exclude patients who are known to have an allergy to dairy products. Cow's milk allergy has an estimated prevalence of 1 in 200 adults.(164, 165)

5.6 Recruitment Process

Patients eligible for the DEFeND REPT were screened through outpatient clinics and weekly Head & Neck Multidisciplinary Team (MDT) meetings. In keeping with a pragmatic approach, this was representative of how patients are engaged during usual care. Patients were not targeted using invitation letters, advertising or incentives.

The steps that were completed on all patients to ensure they met eligibility criteria included:

- Clinical examination
- Detailed medical history including previous treatment to the head & neck
- Clinical decision to offer a lateral neck dissection

Research staff at site documented the outcome of screening assessments in a secure online "Screening log" managed by LCTU. This was an electronic log found in the LCTU portal that investigators were given access to during the SIV. The log generated a screening number and recorded the patient's initials, the date they were approached, the date they were screened, who screened them, the date of randomisation and reasons provided if they were not randomised.

There were no restrictions regarding concomitant care or interventions during the trial. Eligible patients were approached within the outpatient clinic setting and provided with a full explanation of the trial. Patients also received an up-to-date version of the Patient Information Sheet (PIS) (see A.2). Once the patient had the opportunity to read the PIS, ask any questions and agree to participation they were consented to the trial (see A.3 Patient Informed Consent Form (ICF)).

The removal of the (24 hour) cool-off period prior to signing the ICF was agreed by the REC; patients were simply given as much time as they needed. The rationale for such an approach was to reduce patient burden; the recruiting hospitals both provide centralised service for HNS with many patients travelling long distances to attend appointments. In keeping with a pragmatic approach, every effort was made to harmonise the research process with standard clinical care. Removal of the cool-off period enabled patients to avoid extra hospital visits and provide informed consent on the day of being approached if they wished. No patients were asked to provide informed consent on the day of surgery.

The DEFeND REPT piloted a novel way of authorising ICFs electronically. The previous approach required sites to send the signed ICFs to the LCTU via facsimile. The LCTU would authorise the ICF and store the hard copy in a secure location within the UoL. Facsimile is a diminishing technology and has been superseded by electronic transfer of documents. The new method required sites to scan and securely upload a PDF of the signed ICF to the LCTU's online portal using the patient's unique trial number as the file name (see section 4.3.1.1 and B.1 Screening Form for further details). The ICF was checked by two independent members of the central trial team and assessed for validity (checking version number, completeness, signatures and dates). Once validated, the assessors electronically signed-off the relevant eCRF and the uploaded PDF was permanently deleted (see section 4.3.2 and B.6 Randomisation Form for further details). This meant the only evidence for consent was the original hard copy stored in the patient's medical records. This approach left no patient identifiable documents stored within the LCTU/UoL premises.

Once informed consent was given by the patient, site research staff entered baseline data into the eCRF. The following electronic checks needed to be completed before the software allowed the patient to be randomised:

- Eligibility criteria had been entered and electronically signed-off by the principal investigator (PI) (see B.2 Eligibility Form).
- The signed ICF had been uploaded, validated and electronically signed-off by 2 independent LCTU staff (see B.6 Randomisation Form).

5.7 Allocation

Randomisation lists were computer generated by the statistician prior to the recruitment of the first patient. Patients were randomised using a 1:1 ratio. Lists were produced based on the principle of randomly permuted blocks with random block sizes of two and four. Using permuted blocks helped assign the two arms to equal numbers of patients. Each block comprised two or

four randomly ordered allocations with an equal number of patients receiving each allocation.(166) Tables comparing the baseline characteristics of patients and their surgery were produced to evaluate the balance between treatment arms. Continuous variables were summarised as medians with associated inter-quartile ranges (IQR) and categorical variables were summarised as frequencies of counts and associated percentages.

Surgical interventions are complex not only because of the nature of the intervention itself but also the influence of external or associated factors. Figure 17 shows the main constituent elements of a surgical intervention taken from the review by Cook.(138) This figure demonstrates that the outcome of a surgical intervention may be influenced by the surgeon and their operative team as well as the standard of perioperative care. Patients were stratified according to the hospital in which they received their treatment to ensure that variations of surgical teams and standards of perioperative care between sites did not lead to unbalanced randomisation. Kernan et al reported that stratification can protect against type I and type II errors in trials of less than one hundred participants.(166) An important caveat to this advantage is to keep the number of strata as small as possible. This improves statistical efficiency by making it more likely that equal numbers of patients are assigned to each allocation.(166) This approach to randomisation using permuted blocks and stratification according to site was considered the most appropriate way of ensuring balance between treatment arms in a study of this size. A definitive trial will have more participants and may benefit from further stratification such as the extent of surgery as mentioned in sections 5.5.1.2 and 5.5.2.2.

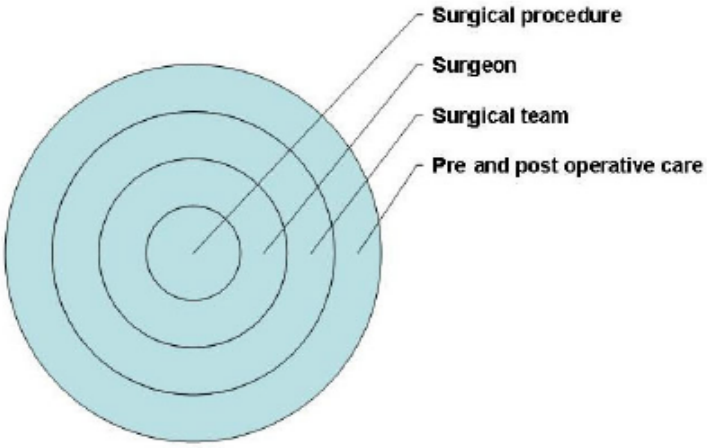


Figure 17 Main constituent elements of a surgical intervention taken from Cook(136)

Based on the LCTU's experience of trials that randomise intra-operatively (PANasta Trial (133)), randomisation for DEFeND REPT was undertaken pre-operatively (see section 3.2.3.3 for rationale). Randomisation was performed by the trial co-ordinator (PhD candidate) using the "Treatment Allocation RanDomIsation System" (TARDIS) software version 3.8. The allocation was concealed to everyone including the person performing the randomisation. Once randomisation had been performed, the surgeon caring for the patient received an automated email which contained a password protected link to reveal the allocation (see B.6 Randomisation Form). Once the patient had undergone their ND and immediately prior to the point of wound closure, the surgeon opened the link to reveal the allocation. The exact time and date the reveal occurred was automatically recorded in the eCRF and cross-referenced against the start and finish times of surgery as a quality assurance step to minimise performance bias.

5.8 Blinding

Patients, outcome assessors, ward staff and research staff (both centrally and at site) were blinded to the allocation. Only members of the surgical team present in theatre when the allocation was revealed knew which treatment arm the patient had been allocated to. These

individuals were not permitted to inform colleagues or assess trial outcomes. The operation notes, medical case notes and any other documentation that left the operating theatre were not allowed to state the allocation. The surgical team was asked to enter the details of surgery on a paper CRF that was later transcribed into the eCRF by site research staff (see B.7 and B.8 Day of Surgery Forms). This included a list of clinicians who were present in theatre at the time of the allocation reveal. If one of these clinicians later assessed an outcome the eCRF would alert research staff of a breach in protocol. The effectiveness of this blinding strategy was assessed at the patient's last visit using blinding indices (see section 5.12.3).

The patient was unblinded if they suffered a SAE and knowledge of the allocation was required for the ongoing clinical management of the condition. The requirement for unblinding was very unlikely as FS is administered only once in the theatre environment. A severe hypersensitivity reaction, air embolism or transmission of an infective agent constituted a SAE. If these did occur, severe hypersensitivity and air embolism would have occurred during or immediately after administration of FS in the theatre setting. Staff caring for the patient at this time would not be blinded so there would not be a delay in diagnosis and emergency management.

If the patient was diagnosed with an infectious disease that was not diagnosed pre-operatively, they would be unblinded. Based on the 'Serious Hazards of Transfusion' 2017 annual report(167) the following infectious diseases are known to have been transmitted via blood products in the UK:

- Hepatitis A, B, C or E
- Human Immunodeficiency Virus
- Parvovirus (B19)
- Cytomegalovirus
- Human T-cell Lymphotropic Virus types I and II
- Malaria
- Variant Creutzfeldt-Jakob Disease or any other prion disease

If the patient was newly diagnosed with any of the above infectious diseases, they would be unblinded and immediately referred to the appropriate medical specialists for treatment.

5.9 Storage, Preparation & Administration of Fibrin Sealant

The DEFeND REPT used the 2ml pre-filled double chamber syringe preparation of ARTISS FS manufactured by Baxter Healthcare LTD. ARTISS was chosen because of its low thrombin concentration that allows surgeons the time to manipulate the tissues before the polymerisation is complete (see section 1.4.3).

5.9.1 Storage protocol

ARTISS has a shelf life of 2 years and should be stored in its protective packaging and transported in a frozen state at less than -20^{o}C.(51)

5.9.2 Preparation protocol

The “Quick Thawing” technique, as described by the manufacturer, was used to prepare the FS for use. Quick Thawing is done by placing the FS in a sterile water bath at 33°C to a maximum of 37°C for 5 minutes. An infrared thermometer is used to check the water temperature prior to immersing the FS. Once thawed the FS may be stored at 33 – 37°C for a maximum of 4 hours. Inspection of both chambers after thawing should reveal clear or slightly opalescent viscous liquids. Solutions that are cloudy/discoloured, contain deposits/particulate matter or solidified should be discarded.(51) (See C.1 Quick Thaw Protocol).

The FS is delivered into the wound as a fine spray driven by medical grade air. The “EasySpray” pressure regulator device is setup as per the manufacturer’s instructions (Baxter Healthcare LTD) and the spray pressure set to 1.5 bar. The scrub practitioner uses the Sprayset tubing to

attach the FS syringe to the EasySpray pressure regulator. Precise details on how this is done can be found on the manufacturer's website (http://www.baxterspraysafety.com/uk.html). (See C.2 EASYSPRAY Quick Reference Guide)

5.9.3 Administration protocol

The administration of FS requires at least 3 people including a scrub practitioner, assistant and surgeon. While the FS is being thawed the surgeon should irrigate the wound with 100ml of sterile Normal Saline, dry the wound with sterile gauze swabs, secure the surgical drain and place several resorbable parachute sutures (4 – 6) across the platysma layer. These sutures should be loosely clipped and not tied to ensure good access to the wound. The drain should be held temporarily outside of the wound to ensure the perforations are not occluded by the FS. The prepared Sprayset should not be held any closer than 10 cm to the wound to avoid the risk of air embolism. Once the administration of FS has commenced the surgeon has 60 seconds to deliver up to 2ml and manipulate the skin flaps into position prior to polymerisation. It is therefore important to strictly adhere to the time using a stopwatch. The assistant should retract any structures (e.g. sternocleidomastoid muscle) to ensure the surgeon can reach sheltered areas and administer the FS evenly in a thin layer across the entirety of the wound. Once administration is complete the drain and skin flaps are repositioned, and even pressure applied to the wound (using a large rolled up gauze swab) while the surgeon ties off all the parachute sutures. It is very important that the surgeon does not lift the skin edges up while tying the sutures as this may break any adhesive bond between tissue layers. The surgical vacuum drain should then be activated, and the assistant should maintain pressure on the neck for a full 3 minutes. After 3 minutes clips/staples are used to close the skin edges. When spraying the FS, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of air embolism. (See C.3 Surgical Protocol)

5.10 Surgical Quality Assurance

Surgical interventions are complex because they are associated with multiple interacting components and concomitant 'co-interventions' such as anaesthesia and elements of perioperative care.(110, 138) Furthermore, the same surgical intervention performed by different surgeons on different patients may vary in its execution and subsequent treatment effect. The topic of 'quality assurance' is therefore very relevant to surgical trial design. As mentioned in section 3.2.3.6, there is arguably some conflict between a truly pragmatic trial design that allows investigators the freedom to use the intervention as they would in usual practice, and a surgical trial design that wishes to tightly control the fidelity and standardisation of the intervention. The latter being more in keeping with an explanatory design. Having said this, most trials lie somewhere within the explanatory – pragmatic continuum rather than at the extremes. The aim of the definitive DEFeND trial will be to evaluate the 'real-world' effectiveness of FS in ND through a pragmatic approach. It was therefore appropriate to not enforce tight controls on the delivery of the intervention in the DEFeND REPT. Nevertheless, in order to deliver a trial that evaluates the intervention in a robust and fair manner, some measures that ensured fidelity and standardisation of the intervention were required.(110) When considering these measures, it was important to consider what impact they would have on recruitment and the smooth running of the trial and aim to strike a balance between adequate standardisation and practicality. Given that the definitive DEFeND trial will include multiple centres and investigators of varying levels of experience in delivering surgical trials, reducing complexity was considered advantageous.

Foster et al(168) performed a systematic review of the different mechanisms of ensuring quality assurance in multicentre trials in laparoscopic colorectal surgery. The review found that the different mechanisms included credentialling of surgeons, standardisation of surgical technique and monitoring.(168) The role of each of these quality assurance measures in the DEFeND trial design are discussed.

5.10.1 Credentialling of surgeons

In the context of explanatory trials evaluating a novel surgical technique, credentialling of surgeons may be seen as a vital element in trial design. This is because surgeons need to demonstrate that they have sufficiently stabilised in their learning curve to facilitate a fair evaluation of the novel technique compared to a control. Once a technique has become more widely adopted by a surgical community, it is likely that a proposed trial design would lie more towards the pragmatic end of the continuum and the role for credentialling becomes more nuanced. For example, excluding surgeons the basis of expertise means that the surgical community in which the intervention will be used is not being fully represented.

Within the context of the DEFeND trial, FS is not a novel product and the safety profile is well established. The manufacturers of FS provide instructions that clearly lay out a series of steps on storage, preparation and administration. These instructions were included in the protocols provided in Appendices C.1, C.2 and C.3. Unlike a novel surgical technique, the use of FS does not require the acquisition of new surgical skills. The surgical steps required for the administration of FS (separate to the ND) include administering the FS and the placement and tying of parachute sutures. These additional steps require only basic surgical skills and therefore are within the skill set of any surgeon who is competent to perform a ND. Indeed, performing a ND competently and safely undoubtedly requires the surgeon to demonstrate a greater range of surgical capabilities. Based on this assertion, the DEFeND TMG decided not to implement a specific credentialling step in the trial design. Instead, they took a pragmatic view and concluded that if a surgeon was skilled enough to perform a ND on NHS patients, then they were skilled enough to administer FS in DEFeND.

5.10.2 Standardisation & monitoring of the intervention

Blencowe et al developed a typology for designing surgical interventions based on a systematic review of 80 RCTs evaluating 160 interventions. The typology was informed by how surgical

interventions were described, standardised and monitored within these RCTs. An overview of the typology is demonstrated in Figure 18.

For the purposes of DEFeND, the intervention was described as ‘closure of the ND wound with FS’. If the typology described in Figure 18 is applied, the overall technical purpose of the intervention was ‘reconstruction’. The ND itself was common to both arms of the study and surgeons were permitted to perform it according to their normal practice. In terms of trial design, the only specified difference between the two arms was the way in which the wound was closed. The individual steps of the surgical intervention are detailed in C.3 (Surgical Protocol).

In terms of standardisation, the surgical protocol in C.3 describes exactly how the intervention should be delivered. This protocol was taught to sites at the SIV, and access to an educational video demonstrating the protocol on a live patient was provided to each investigator (See section 5.11 for details). Furthermore, the flow chart shown in C.3 was laminated and displayed in each head and neck theatre across both sites. Each of the nine steps describing the intervention were considered to be important to ensure the intervention was delivered according to the manufacturer’s instructions. However, there were no mechanisms within the trial design to monitor or enforce the delivery of each step. This implies that according to the typology, each step was optional and applied with complete flexibility.

The lack of monitoring (fidelity of the intervention) may be seen as problematic because data on how well surgeons adhered to the protocol may provide valuable information on how to interpret the trial results e.g. enabling comparisons between intention-to-treat (ITT) and per-protocol analyses. At the time of trial design, the TMG thought that the logistical requirements for effective monitoring were prohibitively complex and resource intensive. It was also seen as a very explanatory approach to trial design. Consideration was given to real-time video evidence and an objective marksheet completed by an unblinded investigator.

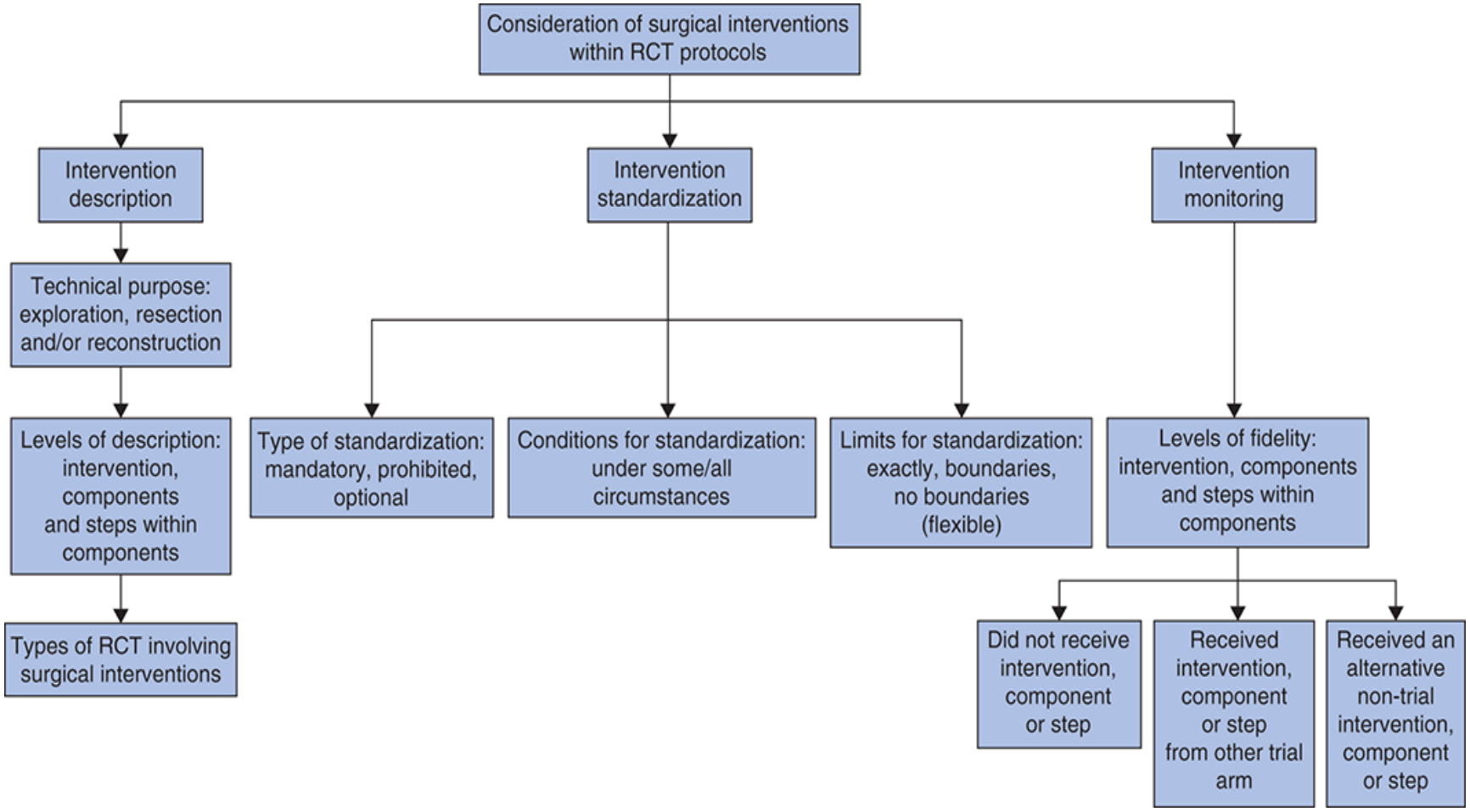


Figure 18 Overview of typology of surgical interventions(108)

Any requirement for video recording would have needed to be included in the PIS and ICF and a clear explanation of how the footage would be stored and disposed of provided. Real-time video evidence may have been recorded by either a fixed operating theatre camera or a mobile camera. Because not all operating theatres have fixed cameras, concerns were raised that this may create a barrier to recruitment/randomisation or lead to missing footage. Commercially available mobile cameras represent a more flexible approach that can be purchased for sites as a research cost (part A; payable through the funder). The video footage could either be uploaded via a 'live stream' or recorded to a memory card. Live stream via a mobile camera requires a very good internet bandwidth and a connection to a smartphone. In the same way that the LCTU considered intraoperative randomisation to be problematic (section 3.2.3.3), live stream would present similar, if not greater, problems. For this reason, recording to a patient specific memory card would have been the most reliable approach. This memory card would have been labelled with the patient's unique trial ID number and stored in the medical records. A major advantage of this approach would be accurate start and finish times of the surgery that may be cross-referenced with the time of allocation reveal. This would ensure that surgeons do not reveal the allocation too early and would be accurate to the nearest minute. Eventually unblinded members of the central trials team would have to evaluate the video footage. The TMG thought that these team members would require some surgical knowledge to appreciate whether the footage was compliant with the protocol. Within the context of a large multi-centre trial, this would result in several hundred hours of video footage that could only be evaluated by a limited number of individuals and was considered to be prohibitively resource intensive.

In hindsight, the resource intensiveness would have been dependent on the amount of detail required from the video footage. For example, if the only information required was whether the FS was applied or not, this could have been determined by fast-forwarding the footage to the wound closure and observing whether the FS was applied. This could have been done by an untrained individual in a matter of minutes.

If monitoring the fidelity of the intervention was undertaken, the steps in the protocol that would have been 'mandatory' were:

- Thawing the FS for five minutes at a temperature between 33 – 37 ^{o}C (confirmed by a reading from an infrared thermometer)
- Setting the EasySpray pressure regulator to 1.5 bar
- Placement of a drain
- Placement of parachute sutures
- Administration of FS
- Repositioning of skin flaps and application of pressure to the wound within one minute of starting the administration of FS
- Application of pressure for three minutes
- Tying off the parachute sutures without lifting the skin edges (and disrupting adhesion)

Under these circumstances, decisions regarding the flexibility of standardization for each mandatory step would be required. Furthermore, there would need to be consensus amongst the TSC regarding what actions should be taken if the intervention was applied outside these parameters e.g. would it constitute a deviation from the protocol and instigate the 'root cause analysis' associated with such an event? Unless the intervention was applied with complete flexibility, the trial design would have moved towards the explanatory end of the continuum.

The other option for monitoring was the completion of an objective marksheet that would be completed by an independent investigator at site e.g. a research nurse. The investigator could have made simple observations regarding the mandatory steps described in the previous paragraph. However, this would have created logistical issues because the marksheet would reveal the allocation to all those who read it. The marksheet would require its own document

pathway to prevent threatening the fidelity of the blinding process, thereby increasing the complexity of the trial. Furthermore, this approach would place greater pressure on investigator staffing levels at sites. Not all sites in a future multi-centre trial will have the capacity to place an unblinded investigator in theatre for several hours whilst also having enough blinded investigators to carry out outcome assessment. Of course, this level of capacity could be made an eligibility criterion for sites to participate in the trial but in doing so, will exclude centres with less resources and push the trial design towards the explanatory end of the continuum. Another significant problem with this approach is that there may be significant interobserver variability in what constituted adherence an/or deviation from the protocol. This would ultimately undermine the value of monitoring.

Whilst both have their own advantages and disadvantages, the use of mobile video camera footage would have been the most likely approach to be chosen. Having a central trial team member evaluate the video footage is a more independent approach and less likely to be biased by inter-observer variability. Including this design feature would have increased the costs and resources required to deliver the trial and therefore, needed to be justified whilst having a positive impact on the interpretation of the results. Within a pragmatic trial design, the outcomes of the ITT analysis are the most important because the prognostic balance between arms afforded by randomization is preserved. The per protocol analysis is an inherently biased interpretation of the results. Therefore, if the per-protocol analysis is going to be disregarded, what is the justification of monitoring the fidelity of the intervention?

The added value of monitoring is that it informs the surgical audience (reviewers and surgeons interpreting data for their practice) of how fair the analysis was and where the problems with the intervention may lie e.g. if the definitive trial outcome was negative, it may have been because either the FS itself was inefficacious or because other elements of the protocol made the FS ineffective. Under circumstances where the trial was negative and the monitoring revealed good compliance with the protocol, one may assume that FS itself was inefficacious. Under circumstances where the trial was negative and the monitoring revealed poor

compliance with the protocol, one may assume that the protocol itself was either flawed or too difficult to follow and hold judgement regarding the efficacy of FS. Whilst the difference between these interpretations is subtle, the latter scenario is still unlikely to convince surgeons or commissioners of care to justify the additional cost of using FS in ND. The extra information afforded by the process of monitoring would certainly be 'nice to know' however, it is debatable whether this information is critical to the interpretation of trial results and therefore may not justify the additional complexities, resources and cost.

5.11 Training

A detailed explanation of the of the protocols for storage, preparation and administration of FS (Appendices C.1, C.2, C.3) was provided during the SIV. Investigators, including recruiting surgeons were given the opportunity to ask questions and raise any concerns with the protocol. Every effort was made to guide sites on how to apply the protocol within their unique environments and practices. In addition to this, sites were provided with access to online educational videos that were produced specifically for the DEFeND trial by the PhD candidate in conjunction with a professional video production and editing company (Aspect Pictures). shown videos during the SIV. These videos used a live patient example to demonstrate the protocol for the preparation and administration of ARTISS as described in section 5.9 and Appendices C.2 and C.3. The first video described the protocol for the preparation of ARTISS and the second described the protocol for administering ARTISS in ND. The online videos were accessed at the web addresses provided below and could have been downloaded by sites if needed. Theatre staff and surgeons who were not experienced with using FS in ND were encouraged to view the videos before the start of surgery.

Part 1: Preparation

https://vimeo.com/442682575

Part 2: Administration

https://vimeo.com/442683279

As discussed in section 5.10.1, surgeon credentialling was not a requirement in the trial design. The educational videos demonstrated how ARTISS should be used but ultimately surgeons were free to use it with complete flexibility. This high degree of flexibility in delivery of the intervention is in keeping with a pragmatic trial design. In addition to educational videos, laminated posters of flow charts summarising the steps of both preparation and administration of ARTISS were displayed in operating theatres as an *aide memoire* (shown in Appendices C.1, C.2 and C.3).

5.12 Randomised External Pilot Trial Outcomes

As this was a REPT, data analyses took the form of descriptive statistics. Continuous variables were summarised as medians (IQR) and categorical variables were summarised as frequencies of counts and associated percentages.

5.12.1 Recruitment & retention outcomes

In the financial year 2019/20 the NIHR awarded over £250 million of funding to 310 research projects.(169) A substantial proportion of this expenditure was invested in RCTs which represent the most powerful research design to evaluate healthcare interventions and guide policy and practice. However, the recruitment of participants to publicly funded RCTs is a frequently reported problem. In a review of 151 RCTs funded by the NIHR Health Technology Assessment (HTA) stream, only 56% achieved their target sample size with a median recruitment rate (participants per centre per month) of 0.92 (IQR 0.43 – 2.79).(170) Problems with recruitment are also reported in HNS trials of which a future definitive DEFeND trial would be one.(105) The potential barriers to recruitment in a future definitive DEFeND trial were discussed in section 3.2.3.1 as justification for a pilot and feasibility study (PFS). In a review of PFS of surgical

interventions funded by the NIHR, Fairhurst et al found that addressing uncertainties around trial recruitment was cited as the most common reason for performing PFS.(124) This is because recruitment is pivotal to the success of a definitive trial and the data from PFS can identify potential recruitment problems and avoid research waste.(120)

Since recruitment is pivotal to the success of a definitive DEFeND trial, it was important to use the REPT to understand why any barriers were encountered. This would enable refinements to the definitive trial design that work to overcome these barriers. For this reason, both quantitative and qualitative recruitment data were collected. The quantitative data indicated what recruitment would be like with the current trial design and the qualitative data indicated what aspects of recruitment required further optimisation and why. Each of the recruitment and retention outcomes is discussed in turn.

5.12.1.1 The proportion of eligible patients randomised to the study

This was calculated as the proportion of screened patients that were randomised. As mentioned in section 5.6, sites were requested to keep a screening log of all potentially eligible patients. This log provided the data for the calculation. If the site did not honour their requirement to keep a screening log, data from theatre records was used to approximate the number of potentially eligible patients.

Based on surgical activity data it was predicted that approximately 180 patients would be potentially eligible over the twelve-month study period across both sites. The recruitment target over this period was 50 patients which could be achieved if 30% of the predicted eligible patients were randomised. Randomising greater than 30% of eligible patients was used as an indicator for effective recruitment.

5.12.1.2 Reasons for failure to screen potentially eligible patients

Qualitative data from unstructured interviews with investigators at sites was used to create a narrative of the difficulties encountered with screening. Holding the dual role of Trial Co-

ordinator and PI for the lead site, the PhD candidate was ideally placed to monitor screening closely. The PhD candidate also had a close working relationship with the PI from the second site to understand any difficulties they faced.

This approach certainly provided useful information but perhaps was not as thorough as it could have been. In hindsight, more granular qualitative data could have been obtained by carrying out a survey and/or semi-structured interviews of all investigators across both sites. There would certainly have been some advantage to understanding the views of all investigators individually, without any potential biases or filters imposed by the PI. For example, the PI may have wished to suppress some views that presented the site in a negative light.

5.12.1.3 Recruitment rate

Recruitment rate was measured as the number of patients randomised per month. This was calculated by simply dividing the number of patients recruited by the number of months the study was open. Calculations for overall recruitment rate and recruitment rate per site were performed as well as recruitment rate for each arm of the study. The same calculations were also performed for the number of patients that were randomised and successfully revealed.

With a recruitment target of 50 patients, it was predicted that at least 4.17 patients would be recruited per month i.e. each site would recruit over two patients per month. Recruiting greater than 4 patients per month was used as an indicator for effective recruitment.

5.12.1.4 Reasons for failure to randomise

For any patient that was eligible but not randomised, investigators at site were required to provide a reason in the free-text box provided within the online screening log (see section 5.6). The various reasons were categorised according to a crude thematic analysis. A bar chart was used to present the frequencies of each theme identified to provide an indication of their relative importance. Numerical values from the bar chart were interpreted with caution and with the

understanding that no inferences could be drawn about the prevalence of phenomena observed beyond the sample.

If the site did not maintain a screening log, data to carry out thematic content analysis was missing. Under these circumstances the PI for that site was contacted for an unstructured interview to understand both why the log was not being maintained and why patients who were eligible were not being randomised. Whilst this provided useful information, it was recognised that this approach was sub-optimal and potentially biased.

5.12.1.5 Number of patients lost to follow-up

This was simply reported as the number of patients who were successfully recruited but did not attend one or more of their follow-up appointments. This data was important to identify any barriers to the retention of patients.

5.12.1.6 Reasons for loss to follow-up

If participants did not attend one of their follow-up appointments, investigators at site were required to contact them and either make a new appointment or ask why they did not attend. As per the PIS, patients were not obliged to give an answer to this question. This qualitative data was analysed using the same methods of inductive thematic analysis described in section 5.12.1.4.

5.12.2 Outcomes related to trial conduct

The rationale behind assessing outcome relating to trial conduct has been discussed in section 3.2.3.5. A key purpose of the DEFeND REPT is to ascertain how well the components of the trial work together in different research environments that may have varying research experience and/or resources.

5.12.2.1 Reasons for failure to reveal the allocation

One of the key learning points from the systematic review reported in Chapter 2 was that performance bias can be reduced by revealing the allocation intra-operatively (see section 2.7). The process of pre-operative randomisation and revealing the allocation at a specific time-point during surgery was novel and previously untested in a clinical trial environment. As mentioned in sections 4.3.2 and 5.7, once the patient was randomised an email containing a password protected link to reveal the allocation was sent to the surgeon caring for the patient. The surgeon was required to access this email and reveal the allocation intraoperatively at the point of wound closure. This process required several design features of the eCRF (MACRO) and randomisation software (TARDIS) to work well together and for the surgeon to access the allocation efficiently. Specifically, the steps in the process were:

- Completion of all pre-randomisation and randomisation eCRFs prior to surgery
- MACRO informing TARDIS that the pre-randomisation checks were authorised by two independent members of the central trial team. The patient's trial specific ID would then be added to a drop-down menu in TARDIS for selection by the investigator delegated to randomise
- Pre-operative randomisation of a specific patient by the investigator delegated to randomise prior to the start of surgery
- TARDIS sending an automated email to the correct surgeon containing a link to reveal the allocation of the correct patient
- The surgeon accessing the link within the email at the correct time point intraoperatively and being successfully able to login and reveal the allocation
- TARDIS communicating the time and date of the allocation reveal back to MACRO

A failure to reveal the allocation at the point of wound closure could be due to a failure of any single, or combination of, the above steps. Compliance with the above steps was monitored by MACRO alerting the data monitor (PhD candidate) if the allocation was not revealed between the start and finish times of surgery. Data on the length of time between the start of surgery and the allocation reveal was also recorded by MACRO. If the allocation was revealed outside the start and finish times of surgery, a deviation from the protocol was noted and root cause analysis instigated (see next section 5.12.2.2 for further details).

5.12.2.2 Protocol adherence

Any deviations from the protocol (including failure to reveal the allocation intra-operatively) instigated a root cause analysis. This was an important outcome of the REPT because it would inform investigators of logistical issues with trial delivery. Once a deviation from the protocol was noted, the PhD candidate completed a corrective and preventative action (CAPA) form. This included a description of the events and their impact on the sponsor, LCTU and trial. The form was completed with oversight from the Quality Assurance Department of the LCTU and corrective and preventative actions proposed along with timelines for completion by a named responsible individual.

Protocol adherence was measured as the number of minor/major protocol deviations observed throughout the study. Details of each protocol deviation were reported from the information provided in the relevant CAPA form.

5.12.2.3 Accuracy of data recording

Having an accurate and as complete dataset as possible is clearly important to the interpretation of the results and study conclusions. The REPT represented an opportunity to evaluate how well sites were able to record data in the eCRF and identify any areas where the trial design prohibited optimal data entry.

Accuracy of data recording was assessed by reporting the type and number of missing data units by treatment arm and site. Possible data outliers were classified as 'mild' or 'severe' based on the following equation:

Mild outliers: *UQ + 1.5 × IQR to UQ + 3 × IQR*

LQ – 1.5 × IQR to LQ – 3 × IQR

Severe outliers: *values more extreme than the above*

(*UQ = Upper Quartile, LQ = Lower Quartile, IQR = Inter Quartile Range*)

If the prevalence of missing data was deemed to be high for a particular outcome measure, investigators at that site were contacted and questioned. This took the form of an unstructured interview led by the PhD candidate to understand why data was missing and how the trial could be designed differently to prevent it.

5.12.3 Fidelity of the blinding process

One of the key learning points from the systematic review reported in Chapter 2 was that detection bias can be reduced by blinding outcome assessors and trial participants (see section 2.7). As discussed in section 3.2.3.3, this is particularly relevant if the outcomes measure is subjective (e.g. severity of signs and symptoms). Evaluating the fidelity of the blinding process was particularly relevant to DEFeND because the operating surgeons were unblinded and there was uncertainty regarding their transfer of bias (intentionally or unintentionally) on to patients and outcome assessors. The methods used to ensure effective blinding are described in section 5.8.

It is widely acknowledged that perfect blinding is practically impossible in any RCT, let alone a surgical RCT. It is therefore relevant to assess the level of blinding that can be achieved for a given trial design. Blinding indices represent an established method of quantifying the level of blinding and use statistical modelling and a respondent's answer to a generic

questionnaire.(171) The level of blinding achieved in the DEFeND REPT was measured to assess whether effective blinding could be achieved. This information would be used to inform the design of a definitive trial.

The two most commonly used blinding indices in clinical trials are by James et al (172) and Bang et al.(173) An important assumption in the James Blinding Index (JBI) is that when a respondent claims to “not know” the treatment allocation, this is an honest answer and not one that is socially desirable or one that avoids making a judgement. JBI is a single index value that combines blinding data from both arms. In practice RCTs can exhibit varying blinding behaviours both in magnitude and direction. The JBI is limited because it cannot distinguish important differences between the arms of a trial.(174)

Whereas JBI places great value on respondents who “don’t know”, the Bang Blinding Index (BBI) sees this as a limitation. Instead, the BBI places greater emphasis on decisive responses which can be in either a positive or negative direction. Furthermore, BBI can be applied separately to each arm of the study and distinguish between nine different blinding scenarios (each of the two arms of the study can be classified as either blinded, unblinded or opposite guessing leading to nine different combinations).(171, 174) The BBI was chosen to evaluate the level of blinding achieved in the DEFeND REPT because it had the potential to provide more granular data on the level of blinding achieved.

In the DEFeND REPT, Respondents had a choice of 5 possible answers: strongly believed they received FS, somewhat believed they received FS, somewhat believe they did not receive FS, strongly believe they did not receive FS and don’t know (see B.12 End of Trial Form). The calculation for BBI produced a numerical value between 1 and -1. A value of 1 implies a complete lack of blinding because respondents always answered correctly; a value of 0 implies perfect blinding because respondents answered correctly and incorrectly an equal number of times; a value of -1 implies ‘opposite guessing’ because respondents always answered incorrectly and may represent a type of unblinding.(173)

Respondents were asked to guess the treatment allocation at the end of the trial. This timing of BBI was chosen because unblinding can occur at any point during the trial follow-up period. Some authors draw a distinction between unblinding due to trial design and unblinding due to of the treatment effects or side effect profile of the intervention.(174) If the intervention is truly effective or has a very different side effect profile compared to the control, participants and investigators can infer the treatment allocation with a high degree of certainty. Under these circumstances a trial can be exceptionally well designed to prevent unblinding but still suffer the consequences of detection bias. In order to detect this phenomenon, Desbiens recommended performing blinding assessments at different time points during the trial.(175) One may have suspected this phenomenon if the results of the blinding assessment performed before any treatment effects became apparent were better than the results of the blinding assessment at the end of the trial. Detection of this phenomenon was not considered relevant to DEFeND because FS has a short half-life and was applied only once during the trial. Furthermore, some of the main treatment effects and side effects of FS (e.g. wound adherence and allergic reactions) have an immediate onset making early blinding assessment impractical.

5.12.4 Determining the minimal clinically important difference in clinical endpoints through semi-structured interviews of trial participants

5.12.4.1 Rationale for determining MCID

As discussed in section 3.2.3.4, the selection of a patient centred primary outcome is critical to the design of a pragmatic trial. There is currently no published core outcome set (COS) for HNS trials to guide this selection in DEFeND. However, a published 'core information set' for HNS provided some valuable insights.(17)

The core information set included "details of drips, drains and tubes" and supports unpublished qualitative data from the 'Aintree Head & Neck Patient Research Forum' demonstrating that patients have an aversion to surgical drains as they are uncomfortable and an impediment to

mobilisation. The ‘core information set’ also included “the likelihood of wound problems” and “details of major or common complications including pain, swelling and bleeding that may require a return to theatre”.(17) Complications after major surgery are a significant cause of morbidity and mortality and have been shown to have a negative impact on long-term quality of life and psychosocial well-being.(134, 135) In surgical oncology, complications can also delay adjuvant RT/CRT which is known to adversely affect survival.(136) The meta-analysis in Chapter 2 also suggested that FS may have a role in protecting patients from complications, albeit not to a statistically significant level and in the face of substantial statistical heterogeneity. Based on these different sources of information, at the start of the trial it was thought that reporting the rate and severity of complications via the Clavien-Dindo classification as a primary outcome measure would be the most pragmatic approach.(23) However, because this decision was inferred from different sources, whether ‘complications’ truly represented the **most** pragmatic and patient centred outcome could not be claimed with a high degree of certainty.

It was thought that the pre-trial inference of using ‘complications’ as the primary outcome could be elucidated by asking trial participants directly what they thought were the most important clinical endpoints and MCID. The process was not conceived or designed to provide an in-depth qualitative analysis that comprehensively explored the patient’s experiences, rather it was hoped that it may provide supporting evidence to use ‘complications’ as a primary outcome. If so, the patient’s views on the MCID would be useful in a future sample size calculation.

5.12.4.2 Qualitative methods

On the final follow-up visit, trial participants were asked what they thought was the MCID in clinical endpoints to justify the expense of FS. In attempt to standardise the way the question was asked, investigators read out the following:

"Fibrin sealant costs approximately £100 per application. Depending on the results of a future clinical trial we may consider introducing fibrin sealant into routine practice for all patients undergoing the same operation that you had.

In your opinion as a patient and taxpayer, what would be the smallest improvement the fibrin sealant would need to offer in a patient's recovery to make it a worthwhile expense?"

This question led to a short discussion where the participant had scope to discuss any issues they wished and was best described as a semi-structured interview. Investigators then summarised the participants response in a free-text box found in the End of Trial eCRF (B.12). The responses were openly coded through a thematic analysing method.(176) Each code attempted to identify and label comments that were relevant to the research question. Patterns within the coded data were identified and overarching themes developed. Each theme was defined and had a central organising concept that unified the data within it. Visual mapping was used to explore the relationship between codes and themes. A narrative summarising the themes was provided leading to a discussion as to whether the findings supported the use of 'complications' as a primary outcome measure.

There are several limitations to the applied qualitative methodology. Firstly, the semi-structured interviews were conducted by untrained investigators in a busy clinic environment. Secondly, the investigators summarised the patient's comments into the eCRF thereby processing the information and potentially applying personal biases (both in the selection and interpretation of what was written). Thirdly, only patients who had completed follow-up were interviewed. It is likely that these patients considered the potential benefits of FS mentioned in the PIS favourably. Patients who did not participate or did not complete follow-up have equally valuable views and opinions that were not collected. Ideally, a separate study conducted by trained investigators using audio recordings of interviews would have provided a much richer and more representative source of qualitative data. Therefore, the findings were not generalisable to patients outside of the current study.

5.12.5 The Relevance of learning curve in a definitive DEFeND trial

5.12.5.1 Methods for evaluating learning curve in surgical trials

Surgical interventions are complex because, as previously shown in Figure 17, the outcome of the intervention may be influenced by several associated or external factors. Furthermore, as discussed in section 3.2.3.6, the fidelity of the intervention and surgical learning curve can have a significant impact on the analysis and outcome of the trial. Surgical learning curve can be defined as an improvement in a surgeon's performance in delivering a novel technique over time.(138) If cases undertaken during a surgeon's learning phase are included in the analysis of a trial, an imbalance in expertise between established and novel techniques may be apparent. This may lead to false estimates of treatment effect and false conclusions against the novel technique (type II error).(177)

Cook defined two distinct, but related, learning curves.(138) Firstly, a technology learning curve related to the iterative process of refining a novel technique. Secondly, a personal learning curve driven by individual surgeon aptitude, training and expertise.(138) The DEFeND trial is a relatively late evaluation of FS in ND given that sprayable forms of FS have been approved for use in the UK since 2014 (see section 1.4.2 for further details).(59) The safety profile and techniques for storage, preparation and administration (described in section 5.9) have become well established over this time. This implies that the technology learning curve is less relevant to the trial design of DEFeND than the personal learning curve.

Cook also described two main options for controlling for learning curve.(138) These were in the trial design by implementing entry criteria for surgeons, and in the analysis of the trial by adjusting for the learning curve effect.(138) The most frequently utilised approach is incorporating expert mentoring and completion of a predetermined number of cases by each recruiting surgeon in the trial design.(178) However, this approach may be problematic because surgeons learn at different rates and their learning may be influenced by external factors. For

example, within the context of a multi-centre trial, different mentoring schemes may result in different learning effects across different centres.(179)

Learning curves can be characterised as having three features: the initial level of performance, the learning rate represented by a non-linear improvement in performance over time, and an asymptote or plateau representing the level at which performance stabilises.(177) Patient outcomes (e.g. complications) or surgical process outcomes (e.g. operative time) can be used as performance proxies by analysing them as a function of the number of cases completed.(180) Patient outcomes are the preferred performance proxy because they directly measure the success of the procedure in improving the health of the patient. However, when the patient outcomes are associated with rare events and/or produce non-continuous data, a prohibitively large number of cases may be required to model the learning effect. Under these circumstances surgical process outcomes may prove more convenient.(181)

Papachristofi et al (182) recommended performing assessments of individual surgeon learning curve using a two-phase model in early studies undertaken before a definitive trial. The two phases being: the learning phase (represented by improvement in performance over time), and final performance level (represented by the asymptotic part of the learning curve). The authors advised using the data from early studies to enable an estimate of the time required by each surgeon to overcome the learning effect. This estimation was based on tracking the performance of surgeons over time.(182) Since different surgeons will reach different final performance levels, Papachristofi et al advocated predefining an expertise level beyond which surgeons are deemed adequately experienced to participate in the trial. To overcome the issue of different surgeons reaching their asymptote at different rates of learning, Papachristofi et al also advocated only initiating an RCT once enough surgeons had reached the predefined level of expertise.(182) Basing a predefined expertise level on the learning curve of small sample of surgeons appears to be an explanatory design feature. A pragmatic trial should seek to include surgeons that have the expertise and aptitude that represents the surgical community in which the intervention will be used. Excluding surgeons who do not meet the predefined level means

that, by definition, the entirety of the surgical community that will use the intervention will not be represented. This is especially the case if the predefined expertise level is set too high. Conversely, if the expertise level is set too low, more surgeons will be included but a proportion of them may still be in their learning phase opening the door to type II error (as described in the first paragraph of this section).(179) Based on this discussion, adopting a predefined expertise level to guide an estimate of the time required to overcome learning effect is equivalent to adopting a 'one size fits all' approach to quantifying learning curve.

The Bayesian hierarchical model described by Cook et al involves adjusting for learning effect in the final statistical analysis.(177) The main advantages of this approach are that there is no need to define entry criteria for surgeons (in keeping with a pragmatic approach), the complex structure of the data can be modelled and the surgeon's prior experience incorporated. Disadvantages include: a lack of power to detect treatment differences at various levels of experience (if a relatively low numbers of cases are performed by each surgeon participating in the trial), modelling is time intensive, a possible increase in type I error if investigating many different performance proxies.(177) Because analysing learning effect has high data requirements, Cook et al recommended using the hierarchical model only if the trial has at least ten participating surgeons who have performed at least ten procedures during the trial.(177)

5.12.5.2 Methods for evaluating learning curve in DEFeND

The learning curve for using FS in ND has not been previously quantified. When designing the DEFeND trial it was not known if using FS in ND was associated with a learning effect and, if it was, how many cases a surgeon needed to perform before they were deemed sufficiently expert. As stated in section 5.10.1 the TMG did not incorporate surgeon credentialling into the trial design. This resulted in surgeons with varying levels of expertise participating in the trial. Although surgeons were provided with access to training resources (see section 5.11), they were permitted to deliver the intervention with complete flexibility. All of these design features were considered very pragmatic but, if a learning effect did exist, they opened the interpretation of clinical outcomes to type II error (as described in section 5.12.5.1). This would obviously be

problematic in a definitive trial but not so much of an issue in the REPT where no formal hypothesis testing was planned.

The DEFeND REPT aimed to recruit 50 patients and would therefore only have data from 25 patients to evaluate the learning curve associated with using FS in ND. As mentioned in section 5.12.5.1, analysing and quantifying learning curve requires much more data. Whilst using the DEFeND REPT to quantify the learning curve may have been unrealistic, simply identifying the presence of a possible learning effect was perhaps more achievable. If evidence for learning effect existed, learning curve would either need to be quantified in a separate pre-trial study or by using the Bayesian hierarchical model in the definitive trial analysis.(138)

In order to identify the existence of a learning effect associated with using FS in ND it was important to establish the prior experience of participating surgeons. From pre-trial interactions with recruiting surgeons, it became apparent that the Ear, Nose & Throat (ENT) surgeons from AUH used FS in ND as a matter of routine. This is evidenced by two articles advocating the use of FS in ND published by their department in 2015 and 2020.(101, 103) The Oral & Maxillofacial (OMF) surgeons from AUH and all the surgeons (ENT and OMF) from QVH did not use FS in ND routinely and, in some cases, had no experience of using it at all. This provided a useful scenario to evaluate the existence of a learning effect since one group had already reached the asymptotic part of their learning curve and the others were at the start or early on. On this basis, the AUH ENT surgeons were classified as ‘experienced’ and all other surgeons were classified as ‘inexperienced’. If the ‘experienced’ surgeons performed better than the ‘inexperienced’ surgeons in the interventional arm and both performed equally in the control arm, the existence of learning effect may be inferred. It is important to note that the term ‘inexperienced’ only referred to the use of FS in ND and did not refer to surgical experience more broadly.

Of course, there may be many reasons why a difference in performance between experienced and inexperienced surgeons might exist. For example, because randomisation was not stratified by surgical specialty, there may be imbalances in patient co-morbidities and how much of

the procedure was performed by trainees. It was also noted that ENT surgeons tend to perform more level II-IV NDs whilst OMF tend to perform more level I-III NDs (based on the primary tumour site and likely nodal drainage patterns). It was postulated that the anatomy of level I may be less conducive to the adhesive effects of FS. The mandible is a rigid structure that moves during function (speech, mastication) that may shear the adhesion of the skin flaps to the underlying muscular wound bed. For this reason, a comparison between NDs involving level I and NDs not involving level I was also made.

The selection of performance proxies was based on patient outcomes of interest and included surgical complications and drainage volume. Surgical process measures were not deemed to be helpful in this analysis because the intervention was delivered at the end of surgery and the manufacturer stipulated that it needed to be delivered within a very specific time frame. Therefore, traditional process measures like blood loss (which would have occurred before the intervention was administered) and operative time were not considered useful discriminators.

1.1 Follow Up

Follow-up was limited to two scheduled visits, the first for the removal of clips at 7-14 days and second for a clinic visit at 4-6 weeks to coincide with the discussion of pathology results. Any unscheduled visits were also recorded in the eCRF. It was important for patients to exit the trial before the start of radiotherapy as this would likely confound their responses to the Patient Reported Outcome Measures (PROM). In keeping with a pragmatic trial design, follow-up was kept to a minimum and tied in with routine postoperative visits. Details on what data was collected at each of these visits can be found in the SPIRIT figure (Table 8)

5.13 Data Monitoring

Formal interim analyses of the accumulating data were performed at 6 monthly intervals after the recruitment of the first patient. A formal Independent Data Monitoring and Safety Committee

(IDMSC) was not convened. In keeping with the guidance outlined in the document 'Guideline in Data Monitoring Committees' published by the Committee for Medicinal Products for Human Use,(183) it was thought that an IDMSC was not required. This is because patients were treated for a very short period (single administration during surgery) and FS is well characterised from a safety perspective and already widely used within healthcare. Although there were potential risks to patients, these were rare and known.

The independent members of the TSC (Chairperson, expert, statistician) took responsibility for reviewing any interim safety data. The independent members were asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justified continuing recruitment of patients or further follow-up. Given this is a REPT, it was anticipated that the TSC would only recommend termination on grounds of safety.

For further details please see A.8 Monitoring Plan.

5.14 Safety

Surgical complications and adverse reactions to fibrin sealant graded Clavien-Dindo IV or above (see Table 1) were the only events reported to assess safety. As the Clavien-Dindo classification constitutes an outcome measure of the trial, the presence of post-operative complications along with their grade was recorded in the eCRF. All complications related to the ND surgery and/or use of FS that were Clavien-Dindo IIIb or below and met the definition of serious were exempt from SAE reporting. Such events were ‘expected’ and were recorded in the relevant section of the eCRF. Post-operative complications related to either ND or use of FS that were Clavien-Dindo IV or above were ‘unexpected’.

The LCTU was required to notify the main REC of all Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study according to the following timelines: fatal and

life-threatening within 7 days of notification; non-life threatening within 15 days. All investigators were to be informed of any SUSARs occurring throughout the study.

Site staff (except for the surgical team) were blinded therefore the SAE reporting form did not state the allocation. For the purposes of SAE reporting, it was assumed that the patient was randomised to the FS arm (i.e. interventional arm). Causality was assigned to the following:

- Anaesthetic
- Generality of surgery (including surgical airway, primary tumour resection)
- ND surgery
- Use of FS

Pregnancy was listed as an exclusion criterion. If a patient became pregnant after recruitment to the trial, there was a requirement to report this in the same way as an SAE. The guiding principles in this event were:

- If the patient had not yet received treatment, or completed treatment, the patient should be withdrawn from the trial.
- Once treatment was complete, i.e. the patient was in follow-up phase, it may be possible to retain the patient to the conclusion of the trial.
- Decisions should be made between the treating clinician and the CI in the best interests of the patient regarding retention in the trial.

For further details please see A.9 Safety Plan.

1.2 Sample Size

As this was a REPT, no formal power/sample size calculation based on clinical data was performed. It was estimated that over the study period of 12 months, approximately 50 patients would be recruited at rate of 30%. Based on this, 50 patients (25 in each arm) would produce a standard error of approximately 6.5% and a 95% confidence interval of approximately (17 –

43%) was be obtained. With respect to surgical complications, being the clinical outcome of current greatest interest, even if a response rate of 50% was observed then a 95% confidence interval of (0.36, 0.64) would be observed which provides enough precision for a future sample size calculation. The future sample size calculation will be performed using intention-to-treat with all available data.

Chapter 6. SELECTION OF DEFINITIVE TRIAL OUTCOMES

The selection of an appropriate primary outcome measure is critical to trial design as it will both define and answer the research question. Furthermore, it will dictate other key aspects of the design such as how data is collected, the frequency and length of follow-up and the sample size calculation. In keeping with a pragmatic design, if the results are to influence clinical practice it is important that the primary outcome measure is meaningful to both patients and healthcare professionals. Ensuring that trials report outcomes that are meaningful is an important rationale for developing a Core Outcome Set (COS). In addition to this, COS address difficulties caused by heterogeneity in outcome measurement and outcome reporting bias within trials.(184) As previously stated there is currently no published COS for HNS. In this regard HNS research falls behind other surgical disciplines. In the absence of a COS, it was thought that 'complications' represented the most suitable and pragmatic primary outcome for DEFeND. This choice was inferred from a core information set(17) and the meta-analysis presented in Chapter 2.

It was hypothesised that there may be some underlying commonality in all COS relevant to surgery. Identifying this commonality may guide what outcomes should be included in the DEFeND REPT. While the specific outcomes will vary across the COS for different surgical disciplines, classifying them into broad themes may provide some useful insight into the research priorities of surgical patients in the broadest sense and identify areas for future development in HNS research. Furthermore, the crude qualitative data collected from trial participants regarding clinical endpoints and MCID may elucidate these findings.

6.1 Review of Surgical Core Outcome Sets

6.1.1 Introduction

The COMET Initiative was launched in 2010 and funded by the MRC Northwest Hub for Trials Methodology. The aims of this initiative were to promote the development and uptake of COS. The COMET Initiative website contains a searchable database of COS that are either in development or published.(185) The aim of the scoping review was to search the COMET Database for surgically relevant COS and identify commonality in themes to guide the selection of outcome measures for DEFeND.

6.1.2 Methods

The COMET Database was accessed via the COMET Initiative website on 02/07/2020: http://www.comet-initiative.org. A review protocol was not prospectively published. The inclusion criteria were: COS For Surgical Interventions; COS designed for use in clinical research; COS developed for any target population; COS published in any year. The exclusion criteria were: patients or their carers were not key stakeholders; COS not published in a peer reviewed journal.

Search criteria that were entered into the search engine were as follows:

Type of intervention: Surgery

Target population: No limitations placed

Methods: No limitations placed

Stakeholders involved: No limitations placed (at this point in search)

Study type: COS for clinical trials or clinical research

Publication status: Published

To increase sensitivity a broad basic search was conducted by entering the word “Surgery” into the “*Search the COMET database*” tab found on the Home page. Duplicates identified through the 2 search strategies were removed and final list limited to: COS clinical research/clinical trials; Published in peer reviewed journal; Stakeholder involvement included Patients OR consumers OR caregivers OR support group representatives OR families OR charities

Data on COS was extracted from the cited publication. Data extraction included: disease name, disease category, study title, year of publication and the list of final COS. The data was summarised in table form. Each core outcome was coded and assigned a theme that was broadly representative of its purpose and nature.

6.1.3 Results

The search yielded a total of 19 COS that met the eligibility criteria. These COS are listed in Table 9. The articles were published between 2014 – 2020 and encompassed a broad range of disease categories. A total of 207 individual core outcomes were identified. The codes used to label each core outcome are shown in Table 10. The broad themes assigned to the codes are also shown in this table. The bar chart in Figure 19 attempts to illustrate the frequency of themes present in all the COS combined.

Table 9 Published surgically relevant core outcome sets registered in the COMET database.

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
Osteonecrosis of the femoral head	Orthopaedics & trauma	How to evaluate the clinical outcome of joint-preserving treatment for osteonecrosis of the femoral head: development of a core outcome set (186)	2019	1) Pain, 2) Range of motion of hip flexion, 3) Walking distance, 4) Stable rating of X-ray images
Prostate cancer	Cancer	Sentinel node biopsy for prostate cancer: report from a consensus panel meeting (187)	2017	1) Sensitivity, 2) specificity, 3) negative predictive value, 4) positive predictive value, 5) false negative rate, 6) false positive rate, 7) number of positive nodes, 8) number of SN outside eLND template, 9) number of patients with metastases to SN only, 10) complication rate, 11) operating time, 12 transfusion rate
Prostate cancer	Cancer, Urology	A core outcome set for localised prostate cancer effectiveness trials (188)	2017	1) Death from prostate cancer, 2) death from any cause, 3) local recurrence, 4) distant recurrence, 5) disease progression, 6) need for salvage therapy, 7) faecal incontinence, 8) bowel function, 9) stress incontinence, 10) urinary function, 11) sexual function, 12) overall quality of life, 13) positive margins,

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
				14) perioperative death, 15) thromboembolic disease, 16) bothersome or symptomatic urethral or anastomotic stricture
Rib fracture, Fractures	Orthopaedics & trauma	An international multi-stakeholder Delphi consensus exercise to develop a core outcomes set (COS) for surgical fixation of rib fractures (189)	2019	1) ARDS, 2) Empyema, 3) Pneumonia, 4) Reintubation, 5) Respiratory failure, 6) iatrogenic mediastinal injury, 7) iatrogenic thoracic injury, 8) iatrogenic vascular injury, 9) mortality, 10) 7 day mortality, 11) 30 day mortality, 12) chronic pain, 13) dyspnoea, 14) lung function, 15) ventilation, 16) pulmonary toilet, 17) disability, 18) physical function, 19) quality of life, 20) HR QoL, 21) return to activities, 22) return to work, 23) invasive mechanical ventilation
Obesity	Endocrine & metabolic	A Core Outcome Set for the Benefits and Adverse Events of Bariatric and Metabolic Surgery: The BARIACT Project (190)	2016	1) Weight, 2) diabetes status, 3) cardiovascular risk, 4) overall quality of life, 5) mortality, 6) technical complication of operation, 7) re-operation, 8) dysphagia, 9) micronutrient status
Perthes' Disease	Orthopaedics & trauma	The outcomes of Perthes' disease: Development of a core outcomes set for clinical trials in Perthes' disease (191)	2020	1) Complications of treatment, 2) pain, 3) activity of daily living, 4) quality of life, 5) family life, 6) psychological impact, 7) school attendance, 8) sleep quality, 9) sports participation, 10) requirement for further surgery, 11) hip

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
				mobility, 12) acetabular coverage and hip congruency, 13) evidence of arthritic change, 14) femoral head shape
Acute Appendicitis	Child health	Core outcome set for uncomplicated acute appendicitis in children and young people (192)	2020	1) Bowel obstruction, 2) wound infection, 3) wound complication, 4) negative appendicectomy, 5) recurrent appendicitis, 6) intra-abdominal abscess, 7) antibiotic failure, 8) quality of life, 9) stress/psychological distress, 10) time away from full activity, 11) length of stay, 12) readmission to hospital, 13) re-operation, 14) death
Perianal Crohn's disease, Crohn's disease	Gastroenterology	Developing a core outcome set for fistulising perianal Crohn's disease (193)	2018	1) Quality of Life, 2) lifestyle restriction, 3) lifestyle restriction based on toileting needs, 4) depression, 5) inability to attend school or work, 6) restriction of sexual activity and avoidance of intimacy, 7) incontinence, 8) score of perianal disease activity, 9) perianal abscess, 10) new/recurrent fistula, 11) unplanned surgical re-intervention, 12) faecal diversion or proctectomy, 13) fistula response on MRI, 14) MRI score responsive to change

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
Cauda equina syndrome	Neurology, Orthopaedics & trauma	Cauda Equina Syndrome Core Outcome Set (CESCOS): An international patient and healthcare professional consensus for research studies (194)	2020	1) Incontinence of urine, 2) urinary retention, 3) sensation of bladder fullness, 4) faecal incontinence, 5) physical ability to have sexual intercourse, 6) perianal sensation, 7) sensation in genitals, 8) leg muscle strength, 9) pain due to abnormal sensation or non-painful stimulus, 10) complications including 11) death, 12) global QoL, 13) occupational role functioning, 14) social functioning, 15) ability to do daily activities, 16) mobility and walking, 17) low mood and depression
Hirschsprung's disease	Gastroenterology	NETS1HD study: development of a Hirschsprung's disease core outcome set (195)	2017	1) death, 2) long-term faecal incontinence, 3) objective score of bowel function, 4) unplanned re-operation, 5) long-term voluntary bowel movements, 6) long-term psychological stress, 7) long-term urinary incontinence, 8) QoL, 9) need for permanent stoma, 10) enterocolitis
Haemorrhoids	Gastroenterology	European Society of Coloproctology (ESCP) Core Outcome Set (COS) for haemorrhoidal disease: An international	2019	PROM of 1) SYMPTOMS to include: blood loss, pain, prolapse, itching, soiling. Secondary outcomes are complications: 2) incontinence, 3) abscess, 4) fistula, 5) urinary retention, 6) anal stenosis. 7) Recurrence, 8) Patient satisfaction

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
		Delphi Study among healthcare professionals. (196)		
Gastroschisis	Child health, Gastroenterology, Neonatal care	Development of a gastroschisis core outcome set (197)	2018	1) Death, 2) sepsis, 3) growth, 4) number of operations, 5) severe GI complications, 6) time on parenteral nutrition, 7) liver disease, 8) QoL
NA	Rehabilitation	What outcomes are important in the assessment of Enhanced Recovery After Surgery (ERAS) pathways? (198)	2015	1) Complications, 2) GI recovery, 3) pain control, 4) global recovery, 5) hospital stay, 6) activities and participation, 7) HRQoL, 8) readmissions
Cardiovascular Disease	Heart & circulation	A core outcome set for adult cardiac surgery trials: A consensus study (199)	2017	1) Mortality, 2) QoL, 3) Hospitalisation, 4) Cerebrovascular complications
Hip Fracture	Orthopaedics & trauma	Developing a core outcome set for hip fracture trials (200)	2014	1) Pain, 2) ADLs, 3) Mobility, 4) HRQoL, 5) Mortality

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
Breast reconstruction	Breast surgery	Development of a core outcome set for research and audit studies in reconstructive breast surgery (201)	2015	1) implant related complications, 2) flap related complications, 3) major complications, 4) unplanned surgery for any reason, 5) donor site problems/morbidity, 6) self-esteem, 7) emotional well-being, 8) normality, 9) QoL, 10) physical well-being, 11) women's cosmetic satisfaction
Oesophageal cancer	Cancer	Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery (202)	2017	1) overall survival, 2) in hospital mortality, 3) inoperability, 4) need for another operation, 5) respiratory complications, 6) conduit necrosis and anastomotic leak, 7) severe nutritional problems, 8) the ability to eat and drink, 9) problems with acid indigestion or heartburn, 10) overall QoL
Arthritis	Rheumatology	Outcome Domains and Measures in Total Joint Replacement Clinical Trials: Can We Harmonize Them? An OMERACT Collaborative Initiative (203)	2015	1) Pain, 2) function, 3) satisfaction, 4) revision, 5) adverse events, 6) death, 7) cost, 8) patient participation
Colorectal cancer	Cancer	Core Outcomes for Colorectal Cancer Surgery: a consensus study (204)	2016	1) Long-term survival, 2) cancer recurrence, 3) resection margins, 4) anastomotic leak, 5) perioperative survival, 6) surgical site infection, 7) stoma rates

Disease Name	Disease Category	Study Title	Year	List of Core Outcomes
				and complications, 8) conversion to open operation, 9) physical function, 10) sexual function, 11) faecal incontinence, 12) faecal urgency

Table 10 Description of domains used to clasify core outcomes

THEME	CODE
Humanistic	1. HRQoL / QoL 2. Patient reported symptoms / outcomes 3. Pain 4. Psychological well being 5. Patient satisfaction 6. Activities of Daily Living (ADL) 7. Ability to work / attend school
Complications	1. Surgical complications 2. General complications and morbidity
Measurements	1. Blood tests 2. Physiological tests (lung function) 3. Physical measurements (range of motion, distance walked) 4. Pathology 5. Imaging 6. Risk assessment (cardiovascular risk scores)
Resource use	1. Returns to theatre 2. Need for further (invasive) treatment including interventional radiology, intubation, mechanical ventilation 3. Operative time

	4. LoS 5. Admission/Readmission to hospital 6. Financial 7. Need for blood transfusion
Mortality	

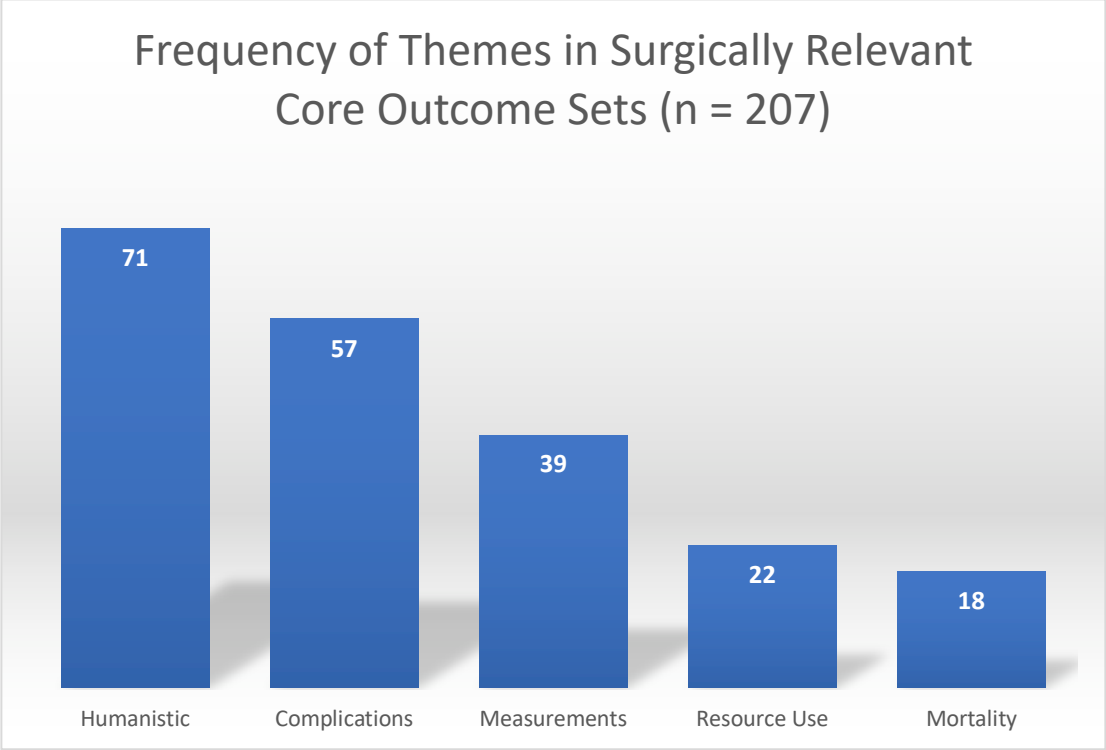


Figure 19 Bar chart demonstrating the number of core outcomes assigned to each domain

6.1.4 Discussion

The results of this scoping review demonstrate that humanistic outcomes and complications are well represented in surgically relevant COS. Humanistic outcomes can be defined as those that are of interest to patients and include symptom status, functional status and QoL.(205) PROMs are integral to the measurement of humanistic outcomes as they allow the patient to

express their unique perspective on health and well-being.(206) Complication outcomes can be defined as those that report adverse events that occur during or after surgery. Traditionally complications are Clinician Reported Outcome Measures (ClinROM) because they require a clinician to examine the patient and make a diagnosis. However, instruments like the Wound Healing Questionnaire (WHQ) developed for the Bluebelle study have demonstrated that complications like SSI can be successfully reported with the use of PROMs (see section 6.2.2.2 for further details).(149) Both humanistic and complication outcomes can be considered 'subjective' outcomes because they require an individual to express their views, whether that is a patient describing their own health status or a clinician diagnosing a complication. Often these outcomes are reported on a severity scale e.g. pain VAS or Clavien-Dindo classification.(206)

Measurements, resource use and mortality can be considered objective measures because they are not subject to the same degree of individual interpretation.(206) Measurement outcomes are those that require the patient to undergo a 'test' that is reported objectively e.g. blood or physiological tests. To some extent pathology and radiology reporting may also be considered subjective outcomes. However, the degree of subjectivity may be minimised by having clearly defined diagnostic criteria. Resource use and mortality are associated with specific events (or duration of events) that occur during a patient's care. These are often recorded by healthcare providers as part of routine practice.

Because this review only included COS that included patients or carers in the list of stakeholders, the high prevalence of humanistic and complication related core outcomes suggest that they are both important and patient-centred ways of assessing surgical techniques and innovations.

According to the COMET database, a COS for HNC is currently in development. This COS is specifically for clinical trials involving Oropharyngeal Carcinoma (OPC).(207) Whilst the treatment for OPC may involve surgery and there may be some crossover, currently no COS specifically developed for HNS trials exists (either published or in development). A specific HNS COS should include patients who have undergone surgery for HNC irrespective of site.

It is not possible to use the results of this review to second guess what a future COS in HNS would look like. The definite trend towards using subjective outcomes to assess surgical techniques and innovations lends itself PROMs. There are many PROMs that are specific to patients that are undergoing treatment for HNC. However, their focus is primarily on QoL and the symptoms associated with RT and/or CRT. Currently the NDII is the only HNS specific PROM.(208)

One of the problems with using ClinROMs to assess complications (e.g. Clavien-Dindo classification) is that they do not define when a complication becomes significant for an individual patient. This is because the threshold for significance will vary between patients. Using ClinROMs in clinical trials requires investigators to decide the threshold on behalf of all patients (e.g. complications that are Clavien-Dindo grade IIIB or above). A well designed and responsive PROM may be able to provide a much more holistic assessment of a surgical intervention. The WHQ validation work for the Bluebelle study has shown it is possible to merge humanistic and complication outcomes by developing an instrument that can effectively diagnose SSI by patient report.(149)

In conclusion there is a need for a COS that is specific to HNS to guide the development of meaningful outcome measures. Where possible subjective outcomes should take the form of PROMs that can provide a patient centred and holistic assessment of new surgical techniques and innovations.

6.2 Selection of Outcome Measures

The clinical outcome measures and PROMS selected for the DEFeND REPT were based on the findings from previously published research (including the core information set by Maine et al (REF)), the systematic review reported in chapter 2 and the review of COS reported in section 6.1. Where instruments specific to ND or HNS were absent, alternatives were sought from the broader surgical literature. It was understood that these instruments may not have been

appropriately validated for use in DEFeND however, by including them, the feasibility of using such instruments in HNS trials could be ascertained. If using these instruments was feasible, this may highlight a potential unmet need in terms of future methodological research in HNS.

6.2.1 Clinical outcomes

In terms of clinical outcomes, aside from descriptive statistics, informal comparisons between allocated groups were made using difference in medians (IQR) for continuous variables and difference in rates for categorical variables. Statistical comparisons between treatment groups took the form of Wilcox Test for continuous outcomes and Fishers Test/Chi-Square Test for categorical outcomes unless otherwise stated. No formal hypotheses were being tested and the nominal 95% CI and p = 0.05 was used to determine statistical significance. No adjustments for multiple comparisons were made.

6.2.1.1 Clavien-Dindo classification of surgical complications

'Complications' were selected as the primary outcome measure for the DEFeND REPT. The rationale for this decision is discussed in section 3.2.3.4 and is further supported by the findings of the review of surgical Cos reported in section 6.1. The Clavien-Dindo classification is a widely accepted tool to grade the severity of surgical complications (Table 1).(23) Because it is a generic classification, grading is open to interpretation when applying it to specific HNS complications. For example, Monteiro et al found that there was imperfect inter-observer reliability in scenarios where patients underwent a surgical procedure that did not require returning to the operating theatre.(137) To avoid this issue within the context of DEFeND, the severity of common/established complications associated with ND were graded and provided to investigators as a guide to conform to the Clavien-Dindo classification (see Appendix D. Clavien-Dindo Classification of Surgical Complications Adapted to Common Head & Neck Complications). The table in Appendix D. was included in the Protocol (See A.1) for investigators to use as a reference if they had doubts regarding appropriate grading of a complication. Furthermore,

the Post-operative Complication form in the eCRF (see B.9) was designed to mirror the table in Appendix D. by asking investigators to grade the complication based on a description rather than allowing them to freely insert a grade. It was thought that providing a description would help reduce inter-observer variability. For rare complications an 'Other Complications' question was included, however, this required investigators to make their own assessment of the most appropriate grade of complication. An assessment of complications using the Clavien-Dindo classification was carried out at every patient encounter after surgery i.e. every day of the patient's hospital stay and at subsequent scheduled and unscheduled follow-up visits (B.9 Post-operative Complication Form).

Using the original Clavien-Dindo classification shown in Table 1 does not accommodate for the cumulative morbidity of experiencing more than one complication i.e. from a patient's perspective, experiencing multiple minor complications may be just as taxing as experiencing one major complication. The Comprehensive Complication Index (CCI) uses the Clavin-Dindo grade for each complication a patient experiences and produces a numerical value between 0 (no complication) to 100 (death).(209) In patients that experience multiple complications, the CCI uses an algorithm to combine the numerical value of each complication and produce a number for overall morbidity. Further details on the CCI can be found at:

https://www.assessurgery.com/about_cci-calculator/

Slankamenac et al provided external validation for the CCI utilising three previously published RCTs that reported specific complications after different surgical procedures.(210) These complications included pancreatic fistula after pancreaticoduodenectomy, anastomotic stricture after oesophagogastrostomy and overall complications after colonic resection. Slankamenac et al reported superiority of using CCI compared to using specific complications or traditionally reported morbidity endpoints. They found that CCI reduced sample-size by virtue of it being a continuous outcome measure and was closely associated with length of hospital stay, length of ITU stay and in-hospital costs. When calculating the sample size for these trials a MCID of

10 CCI points was used. This was derived from the fact that 10 points reflects one grade of difference in the traditional Clavien-Dindo classification.(210)

The authors of the CCI were contacted for permission to use their tool in DEFeND. The algorithm is copyrighted and was accessed by using their 'online calculator'.

6.2.1.2 Drain outcomes

The drain outcomes collected included:

- Time (hours) for daily wound drainage volume to reach <1.25ml/hr.
- Time (hours) to drain removal (as dictated by drainage volume).
- Total wound drainage volume (ml).

The core information set published by Main et al reported that "details of drips, drains and tubes" was important to patients and other key stakeholders. This is in keeping with unpublished qualitative data from the 'Aintree Head & Neck Patient Research Forum' that demonstrated patients have an aversion to surgical drains as they are uncomfortable and an impediment to mobilisation. However as discussed in section 3.2.3.4, 'Time to drain removal' is a very short-term outcome measure and using it as a primary outcome measure in the DEFeND trial would move away from a pragmatic design.

The decision to remove a drain is often a clinical decision based on the volume and appearance of the drainage fluid. Surgeons often use various arbitrary volume thresholds in the decision to remove drains based on a balance of risk between retaining drains long enough to prevent fluid collections and removing them before they instigate SSI, none of which are particularly evidence based. Using 'time to drain removal' as a primary outcome measure may require standardisation in the protocol to minimise bias and make results comparable between patients. However, in doing so, the trial becomes more explanatory in nature.

Section 1.3 provided some background to surgical drain practices in ND. The threshold for drain removal is based on a balance of risk between retaining drains long enough to prevent fluid collections and removing them before they instigate SSI. The majority of surgeons in North America use volume as the main indicator for drain removal with 30ml in a 24-hour period being the most popular threshold.(35, 36) The threshold of 30ml/24hrs is also common amongst different surgical specialties working in different anatomical areas but there is a surprising lack of objective evidence supporting it.(39, 40) However, there is considerable variations in practice with some authors advocating higher volume thresholds and/or measuring drain volumes more frequently.(41-44)

In a pragmatic design it is important that trial outcomes are generalisable (external validity). There is currently no published UK based consensus on the most appropriate threshold for drain removal and number of drains used in ND. Based on the perception that UK HNS practice tends to be similar to North American practice and that the purpose of a drain is the same irrespective of the clinical setting, a threshold of 30ml in a 24-hour period was chosen and use of only one drain permitted. Anecdotally, this threshold and number of drains corresponds to the PhD candidates experience of working for different Head & Neck Surgeons in the UK throughout his training. It is recognised that carrying out a pre-trial survey of UK Head & Neck Surgeons to establish whether there was consensus amongst respondents would have been a more robust approach to defining the threshold and number of drains.

When designing the trial, it was considered important to ensure some standardisation in the way drain volumes were recorded. At that time, taking the decision to remove the drain away from surgeons was though to minimise detection bias. On that basis the following drain protocol was stipulated:

- Use of a single size 18 HandyVac^{TM} drain. This drainage system by ConvaTec has a collection bag with a tap for emptying contents as shown in Figure 20.

- Drain volumes were recorded at least twice daily (morning and evening) and the contents of the drainage bag were emptied into a measuring cylinder for precise measurement.

- Drain volumes were entered in the eCRF in real time. As described in section 4.3.4.2, the eCRF was programmed to calculate the rate of drainage (volume/time) and inform investigators whether the drain should be removed using the algorithm shown in Figure 15 (also see B.10 Drain Output Data Form).

- It was thought that estimation of drain volume using the scales found on drain bottles and bags would result in significant interobserver variability and was not precise enough for the drain removal algorithm in Figure 15.

Figure 20 HandyVac(TM) wound drainage system by ConvaTec

In retrospect, measuring drain volumes and stipulating a specific drain protocol were very explanatory design features. In a future definitive trial, alternative approaches will need to be sought. In a pragmatic design, surgeons should be allowed to remove the drain based on their own practice. For this approach to produce fair and meaningful results, consideration needs to be given to stratification of randomization and how effectively outcome assessors are blinded to the allocation. For example, strata could be based on site if there was agreement that drain practices would remain identical within each site. Alternatively, strata could be based on individual surgeon practices irrespective of site. The latter approach would benefit from a pre-trial

survey of recruiting surgeons to establish all combinations of drain removal thresholds and numbers of drains used. If drain practices are highly variable, stratifying based on individual surgeon practice may be problematic if infrequent practices do not recruit enough patients (see section 5.7 for further explanation). In both scenarios surgeons would need to understand that the same protocol would apply for both interventional and control arms. The effective blinding of outcome assessors is vital to producing unbiased results as discussed in section 3.2.3.3.

6.2.2 Patient reported outcome measures

According to the review of surgical COS reported in section 6.1, humanistic outcomes have an important role if surgical research and PROMs are integral to their measurement. The inclusion of PROMs in DEFeND was thought to be important however, it quickly became apparent that there was a paucity of instruments validated specifically for HNS.

6.2.2.1 Neck Dissection Impairment Index

The NDII was chosen because it is the only validated ND specific health related quality of life (HRQoL) instrument.(147) Other similar instruments include 'Disability of the Arm, Shoulder and Hand' (DASH)(211), 'QuickDASH'(212), 'Shoulder Pain and Disability Index' (SPADI)(213) and the University of Washington Quality of Life (UW-QoL) shoulder subscale.(214) Doctoral research from the Nova South-eastern University entitled 'Shoulder-Specific Patient Reported Outcome Measures for Use in Patients with Head and Neck Cancer: An Assessment of Reliability, Construct Validity, and Overall Appropriateness of Test Score Interpretation Using Rasch Analysis' concluded that NDII was the most appropriate instrument for patients with HNC.(215)

Appendix B.4 shows the NDII eCRF and provides details on the questions patients were asked. The raw scores were standardized to a value that was a fraction of 100 according to the original publication using the following equation:

$$\text{Standardized score} = [(\text{raw score} - 10) / 40] \times 100$$

The NDII is validated for use in patients who have undergone selective or modified radical ND and in the validation research, was used eleven months post-operatively.(147) However in the DEFeND REPT, patients undertook a baseline NDII pre-operatively and another at Follow-up visit two (4 - 6 weeks). Although the NDII is not validated for use 4 - 6 weeks after surgery, there is evidence that the NDII score at this early juncture is representative of longer-term HRQoL.(216) In a recently published RCT, NDII was used as the primary outcome measure six months after surgery. The authors of this RCT quoted evidence from the physiotherapy literature that demonstrated that the majority of shoulder function recovery after ND is complete by this point. An MCID of 18.1 points was used in the sample size calculation of this RCT based on a telephone survey of 25 patients who had undergone ND.(217) If the NDII is to be used in a definitive trial, consideration for extending the follow-up period to a minimum of six months must be considered.

6.2.2.2 Wound Healing Questionnaire

The WHQ is not validated for HNS however it was felt important to include this instrument to understand how it can be applied to HNS trials. It has already been proposed that complications represent an important patient centred outcome in HNS specifically and surgical research more broadly. However, instruments like the Clavien-Dindo classification and CCI are not without fault and are not specific to HNS. The WHQ was developed and validated for use in the Bluebelle study; a feasibility study of different wound dressing strategies for the prevention of SSI in elective and unplanned abdominal surgery.(149) Whilst its specific application is not relevant to DEFeND, the WHQ represents a PROM that can effectively diagnose a surgical complication. In addition to diagnosis, the PROM allows the patient to express their unique perspective on their experience of said complication(s). It was felt that if the WHQ was successfully deployed in DEFeND, a strong argument can be made for the development of a similarly designed HNS specific instruments in the future.

Colleagues involved in designing and validating the WHQ from the University of Bristol were contacted, and permission sought to include the WHQ in the DEFeND trial. Permission was

given on the provision that anonymized and contemporaneous data on WHQ as well as the clinician diagnosed validation used in the original study was sent every month. Patients recruited to the DEFeND study completed the WHQ at Follow-up visit two (4-6 weeks). Appendix B.13 demonstrates the questions that patients were asked when completing the WHQ. The clinician diagnosed validation questions requested by the Bluebelle study team were based on the Centres for Disease Control and Prevention (CDC) criteria of SSI and shown in Appendix B.14. Blinded clinicians assessed the patient using the CDC criteria at visit two.

As already mentioned above, the WHQ was not designed for use in HNS trials and has not been validated in HNS patients. Whilst there was no intention to validate the WHQ within the small DEFeND REPT, it was thought that using the data that was requested by the Bluebelle study team to perform our own basic assessment may provide some insight into how successful an instrument like the WHQ would be in a HNS trial. The patient responses to the WHQ in DEFeND patients was examined against a clinician diagnosis of SSI. The clinician diagnosis of SSI was recorded as 'no SSI' or 'SSI of any type' and based on the results of the 'face-to-face' assessment form shown in Appendix B.14. 'Sensitivity' and '1 – specificity' values of WHQ for different thresholds were used to plot a receiver operating characteristic (ROC) curve. The performance of the WHQ to discriminate between patients who had SSI and those that did not was measured by the area under the curve (AUC). An AUC value approaching 1.0 indicated good discrimination, whereas a value approaching 0.5 indicated poor discrimination.

6.2.2.3 Neck pain scale

Pain is a commonly reported symptom after surgery(218) and was included in DEFeND as a relatively easy to administer PROM. It was thought that pain may correlate with wound healing and certain surgical complications thereby providing additional information of the role of FS in ND. Originally it was planned to use a visual analogue sale (VAS) to provide a numerical value that was measured between zero and ten. However, this required the use of a paper CRF that patients needed to physically mark. Within the context of an eCRF, investigators found it much easier to administer a Numeric Rating Scale (NRS) and simply ask patients to score their pain

out of ten (zero being no pain and ten being the worst pain possible). The Neck Pain eCRF is shown in Appendix B.5. Pain scores were taken at every patient encounter including baseline, every inpatient day and all scheduled and unscheduled follow-up visits.

Chapter 7. RESULTS

7.1 Description of Baseline Subject Characteristics

The baseline measures of variables that were considered important/relevant are presented in Table 11. The inclusion of patients who had previous treatment to the neck was considered an important and pragmatic design feature however, only nine such patients were recruited. The three patients who had previous ipsilateral or contralateral radiotherapy were in the 'No FS' arm, and the three patients who had previous neck surgery were in 'FS' arm. Three patients were reported as previously having 'Other Neck Treatment' (2 from QVH, 1 from AUH) but in all cases further details were not provided.

Whilst every effort was made to include patients at high-risk of complications, most patients were low risk. A minority of patients had previous treatment to the neck (18%), were current smokers (16%), were immunosuppressed (2%), anticoagulated (12%) or on antiplatelet therapy (6%).

The 'No FS' arm had five patients with a Performance Status (PS) of 2 and one patient with a PS of 4. The 'FS' arm had no patients with a PS >1. Overall, this suggests that patients in the 'FS' arm were better functioning before surgery.

Table 11 Baseline demographics

Covariate	Level	Fibrin Sealant (n=26)	No Fibrin Sealant (n=25)	Total (n=51)
Previous Neck Treatment	No Previous Treatment	21 (81%)	21 (84%)	42 (82%)
	Ipsilateral RT	0 (0%)	1 (4%)	1 (2%)
	Contralateral RT	0 (0%)	2 (8%)	2 (4%)

Covariate	Level	Fibrin Sealant (n=26)	No Fibrin Sealant (n=25)	Total (n=51)
	Ipsilateral ND	2 (8%)	0 (0%)	2 (4%)
	Ipsilateral Open Biopsy	1 (4%)	0 (0%)	1 (2%)
	Other	2 (8%)	1 (4%)	3 (6%)
Height	median (IQR)	1.78 (1.755, 1.828)	1.7 (1.65, 1.78)	1.77 (1.685, 1.795)
Weight	median (IQR)	84.7 (74.275, 99.55)	71.4 (65.8, 83.4)	81.3 (70.9, 89.5)
BMI	median (IQR)	27.55 (25.402, 31)	25.94 (24.5, 28.8)	26.91 (24.565, 29.725)
WHO Performance Status	0	19 (73%)	17 (68%)	36 (71%)
	1	7 (27%)	2 (8%)	9 (18%)
	2	0 (0%)	5 (20%)	5 (10%)
	4	0 (0%)	1 (4%)	1 (2%)
Smoking	Current	4 (15%)	4 (16%)	8 (16%)
	Ex-Smoker	13 (50%)	8 (32%)	21 (41%)
	Never Smoked	9 (35%)	13 (52%)	22 (43%)
Immunosuppressive treatment	No	25 (96%)	25 (100%)	50 (98%)
	Yes	1 (4%)	0 (0%)	1 (2%)
Antiplatelet	No	24 (92%)	24 (96%)	48 (94%)
	Yes	2 (8%)	1 (4%)	3 (6%)
Anticoagulated	No	22 (85%)	23 (92%)	45 (88%)
	Yes	4 (15%)	2 (8%)	6 (12%)
Hb	median (IQR)	143 (133.5, 149)	140 (127.5, 149)	141.5 (128.25, 149)
Platelets	median (IQR)	228 (175.5, 289)	294 (288.5, 342)	288.5 (210.5, 321)
White cells	median (IQR)	6.8 (6.05, 8.75)	8.85 (5.925, 10.3)	7 (6, 9.6)
PT	median (IQR)	10 (10, 11)	10 (10, 11)	10 (10, 11)
aPTT	median (IQR)	25 (24, 26)	26 (25, 28)	25 (24, 27)

Covariate	Level	Fibrin Sealant (n=26)	No Fibrin Sealant (n=25)	Total (n=51)
Randomisation	Randomised but not revealed	1 (4%)	2 (8%)	3 (6%)
	Randomised and revealed	25 (96%)	23 (92%)	48 (94%)

The distribution of surgical characteristics across both treatment arms is presented in Table 12. Again, there is an approximately even distribution of variables. Notable differences include:

1. Three patients had a level I-V ND (modified radical ND) and were all in the 'No FS' arm. Modified radical ND is associated with a larger surgical dead space therefore, this difference favours the 'FS' arm.

2. Patients in the 'No FS' arm had less intra-operative blood loss. Low intra-operative blood loss is often associated with uncomplicated surgery or meticulous surgical technique. This difference therefore favours the 'No FS' arm.

3. Patients in the 'FS' arm had slightly longer operations by approximately 25 minutes. This may be related to the time it takes to prepare and administer the FS.

4. One patient in the 'No FS' arm is reported to have 0 levels of the neck dissected. This was due to an administrative error. The patient in question was a late withdrawal from the trial because they were deemed inoperable during surgery. However, the 'Day of Surgery' eCRF had already been opened and data on the patients ASA entered. The number of levels dissected is automatically populated by the eCRF based on tick boxes (see Day of Surgery Form B.8). In this case the patient had no levels selected and the outcome box was automatically populated with '0'. This patient has not been included in any subsequent analyses. This also explains why the total number of patients in the table is 49 rather than 48.

Overall, the differences between the arms are small and may indeed negate each other. It is therefore assumed that any differences between the treatment arms, both in terms of baseline demographics and surgical characteristics, are not significant.

Table 12 Summary of surgical characteristics by treatment arm

Covariate	Level	Fibrin Sealant	No Fibrin Sealant	Total
Total		25	24	49
Primary Resection	No	10 (40%)	11 (46%)	21 (43%)
	Yes	15 (60%)	13 (54%)	28 (57%)
No. Neck Levels	0	0 (0%)	1 (4%)	1 (2%)
	3	19 (76%)	16 (67%)	35 (71%)
	4	6 (24%)	4 (17%)	10 (20%)
	5	0 (0%)	3 (12%)	3 (6%)
Cutting Instrument	Cold Steel	15 (60%)	18 (75%)	33 (67%)
	Cutting Diathermy	3 (12%)	2 (8%)	5 (10%)
	Harmonic Scalpel	7 (28%)	3 (12%)	10 (20%)
Intra-operative Blood Loss	median (IQR)	100 (40, 100)	50 (25, 100)	50 (27.5, 100)
Length of surgery (hours)	median (IQR)	2.467 (1.942, 2.958)	2.05 (1.683, 2.383)	2.2 (1.775, 2.617)
Time to revealing Allocation (hours)	median (IQR)	2.283 (1.667, 2.6)	2.05 (1.358, 2.375)	2.133 (1.55, 2.5)
Time in Recovery Room (hours)	median (IQR)	1.683 (1.3, 2.35)	1.642 (1.417, 1.987)	1.667 (1.367, 2.083)
Nodal Yield	median (IQR)	22 (17.8, 27.5)	22 (19, 28)	22 (18, 28)

7.2 Pilot/Feasibility Outcomes

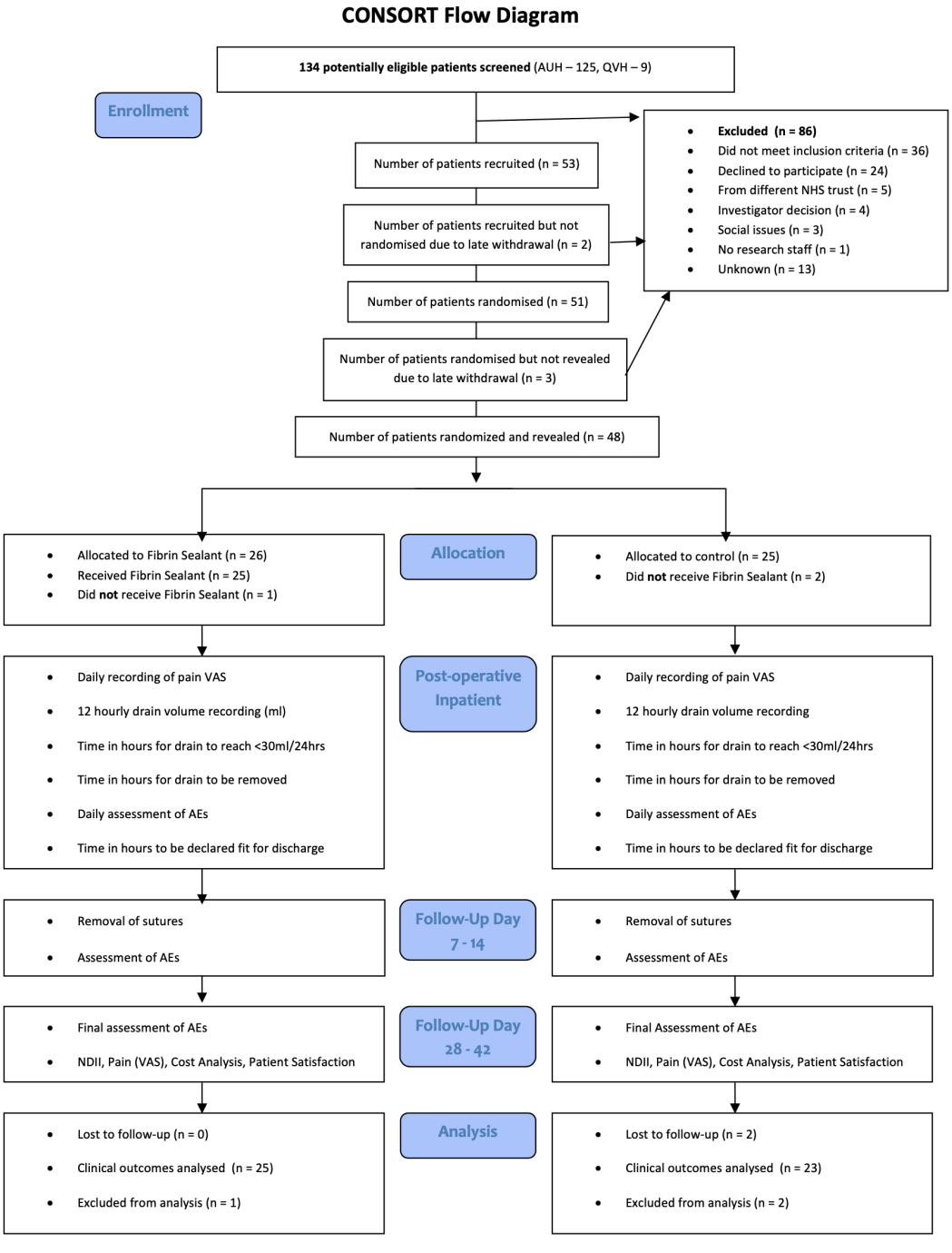


Figure 21 CONSORT flow diagram of the progress through the phases of the study (enrollment, allocation, follow-up, data analysis

7.2.1 Recruitment and retention outcomes

7.2.1.1 Proportion of eligible patients randomised to the study

The CONSORT flow diagram in Figure 21 summarises the progress through the different phases of the study. AUH screened a total of 125 patients. Of these patients 33 did not meet eligibility criteria. Of the 92 remaining patients, 46 (50%) were recruited and 42 (45.7%) were successfully randomised and revealed. For 13 patients the reason for failure to randomise is unknown. On the presumption that these patients did not meet eligibility criteria, the highest possible proportion of eligible patients recruited from AUH is 58.2% (46/79). The highest possible proportion of eligible patients randomised and revealed from AUH is 53.2% (42/79).

QVH screened a total of 9 patients. All 9 of these patients met eligibility criteria. Of these patients 7 (77.8%) were recruited and 6 (66.7%) were successfully randomised and revealed. Data from operative records indicates that 22 potentially eligible NDs were performed at QVH during their recruitment period. On the presumption that all unscreened patients met eligibility criteria, the lowest possible proportion of eligible patients recruited from QVH is 31.8% (7/22). The lowest possible proportion of eligible patients successfully randomised and revealed from QVH is 27.3% (6/22).

Overall, between both sites 134 patients were screened. It is known that at least 33 did not meet eligibility criteria. A total of 53 patients were recruited, and 48 patients were successfully randomised and revealed. Therefore, the overall proportion of eligible patients recruited is 52.5% (53/101). However, based on the missing screening data, this value may range between 31.8% – 58.2% in the definitive trial. Similarly, the overall proportion of eligible patients successfully randomised and revealed is 47.5% (48/101) with a range of 27.3% - 53.2%.

Prior to commencement of the REPT, it was predicted that a total of 180 patients would be eligible over a 12-month period and 30% of these would be randomised. In fact, AUH screened 92 eligible patients over a 10-month period and QVH screened 9 over a 5-month period. Whilst

the observed number of eligible patients proved to be lower than predicted, the study has performed better than predicted in terms of the proportion of these patients randomised.

7.2.1.2 Reasons for failure to screen potentially eligible patients

Qualitative data from unstructured interviews with investigators at sites was used to create a narrative of the difficulties encountered with screening.

AUH has a strong track record of recruiting to Head & Neck clinical trials. This is in part due to engaged clinicians and an active Research Nurse (RN) presence. Prior to the Head & Neck MDT meetings, the RNs 'pre-screen' the electronic records of all the patients to be discussed. All actively recruiting trials that a patient may be eligible for are then recorded adjacent to the patient's details on the MDT list. This serves as an effective *'aide memoire'* for clinicians when making treatment decisions during the meeting. If the clinician agrees that the patient may be eligible, the patient is approached later that day when they attend the outpatient clinic. This highly sensitive process of screening is well established at AUH and would be difficult to improve upon.

Conversely, QVH had difficulty screening potentially eligible patients. However, once patients were successfully screened, a relatively high proportion (66.7%) were successfully randomised and revealed. A possible reason given for this was that QVH does not share the same research culture and infrastructure as AUH. QVH serves as a tertiary surgical 'hub' for several 'spoke' district general hospitals (DGH). HNMDTs are convened at the DGH sites on different days of the week which makes research support more challenging and labour intensive. The spoke DGH sites were not opened, therefore, patients were not allowed to be approached or consented at these sites. Furthermore, QVH does not have the same number of RNs that can support research activity throughout the working week. The relatively high proportion of eligible patients randomised at QVH is by virtue of a pro-active PI. The PI was able overcome many of the infrastructure obstacles by actively engaging his surgical colleagues. However, by his own admission, if he did not engage them, potentially more eligible patients would have been lost.

7.2.1.3 Recruitment rate

A total of 53 patients were recruited to the study but only 48 were randomised and revealed successfully. 3 were randomised but later withdrawn from the study and not revealed, the remaining 2 were recruited but never randomised. Of the 2 that were not randomized only 1 was reported to have an 'unassigned' treatment code in the analysis. The reasons for this are unclear as the correct number of unassigned patients should be 2. In all cases this was due to last minute changes in treatment plan that meant the patient was no longer eligible. Table 13 demonstrates the number of patients recruited by site and Table 14 demonstrates the number of patients who were successfully randomised and revealed by site. The recruitment window differed between sites because AUH was opened first and started recruitment in November 2018 whereas QVH opened for recruitment in February 2019. In total AUH was open for 10 months and QVH for 5 months. The overall recruitment rate for the study was 5.3 patients/month [4.6 patients/month for AUH and 1.4 patients/month at QVH]. This was higher than the predicted 4 patients/month.

Table 13 Recruitment by site

Site	Date of First Rand.	Date of Last Rand.	Fibrin Sealant	No Fibrin Sealant	Unassigned	Total
Aintree University Hospital	2018-11-08	2019-08-28	23	21	2	46
Queen Victoria Hospital	2019-02-04	2019-07-07	3	4	0	7

Table 14 Patients who were successfully randomised and revealed by site

Site	Date of First Rand.	Date of Last Rand.	Fibrin Sealant	No Fibrin Sealant	Total
Aintree University Hospital	2018-11-08	2019-08-29	22	20	42
Queen Victoria Hospital	2019-02-04	2019-06-17	3	3	6

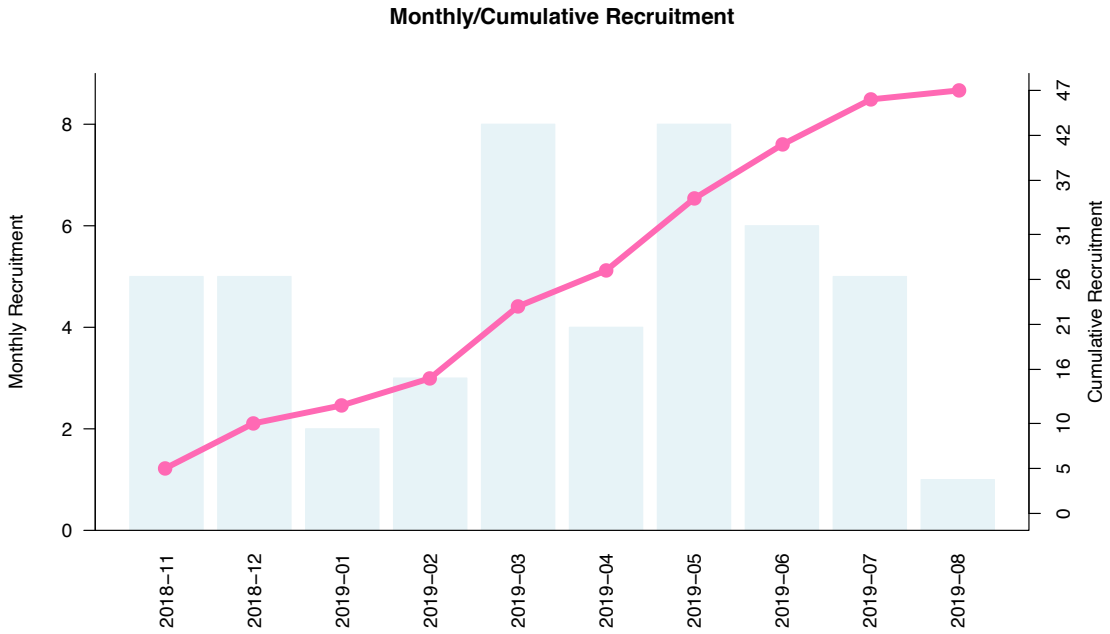


Figure 22 Cumulative recruitment

The cumulative recruitment curve based on monthly randomisation figures is presented in Figure 22. Recruitment was steady across the study period apart from small dip in January 2019 followed by an acceleration in March that corresponded to both sites being opened and recruiting. Recruitment was considered successful because the target of 50 patients was exceeded two months ahead of schedule.

7.2.1.4 Reasons for failure to randomise

The relative frequencies of reasons that patients were not randomised are presented in Figure 23. Both sites saw approximately 22% of patients declining to participate (AUH 22/101 (21.7%); QVH 2/9 (22.2%)).

Only five eligible patients were lost because they were seen in 'spoke' sites that were not open to the study. However, the true number is likely to be higher because QVH faced problems screening patients from spoke sites.

There is some concern regarding the exclusion of patients because of 'investigator decision' and 'social issues'. Four patients were lost because the investigator decided against recruiting the patient to the study. Three patients were lost because the investigator or RNs recruiting the patient felt that the patient's social circumstances were such that they would hinder compliance with the trial thereby moving the trial away from its pragmatic design.

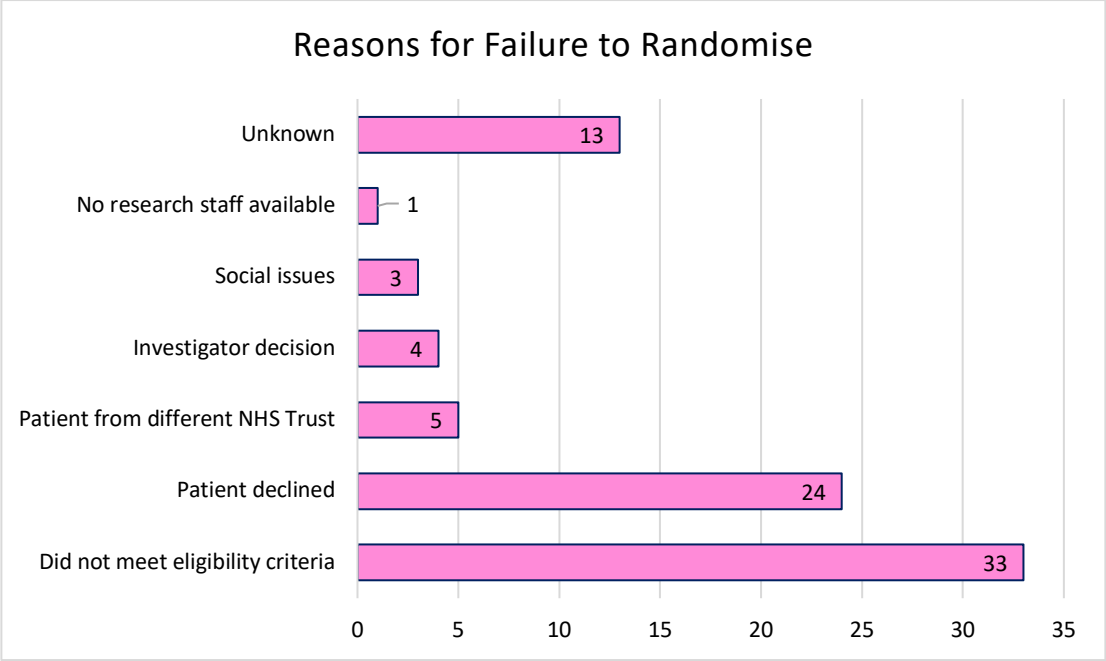


Figure 23 Relative frequency of various reasons for failure to randomise

Whilst recruitment was successful issues were encountered across both sites. Below is a brief narrative of problems by site derived from an unstructured interviews from investigators at site.

QVH recruitment problems

As mentioned previously QVH provides tertiary Head and Neck surgery services to several 'spoke' DGH sites. Patients are seen, diagnosed and treatment planned at these spoke sites. The patient then attends QVH for their surgery. This model provides administrative barriers to recruitment because each spoke sites needs to confirm 'capacity and capability' and undergo the 'green light process' to open the trial. Because this process can take several weeks, and the recruitment window for QVH was already shortened, a decision was made not to open the spoke sites.

The trial protocol stipulated the use of a single surgical drain. This was a requirement of the drain protocol described in section 4.3.4.2 (drain output data form) and 6.2.1.2 (drain outcomes). Some surgeons at QVH voiced concerns over the use of a single drain as this was a deviation from their normal practice of using two drains. These surgeons were primarily concerned about complications and their medicolegal sequelae. They asked that the investigators provide evidence to support the use of a single drain. Even though this evidence was duly provided, these surgeons did not recruit any patients to the trial.

AUH recruitment problems

Overall AUH did not struggle to recruit patients. However, the proportion of eligible patients randomised rate was lower than QVH. A small number of patients were lost because they were from spoke DGH sites that were not open. However, this was less of an issue than QVH because most patients are discussed in the MDT and seen in clinic at AUH prior to their surgery.

7.2.1.5 Number of patients lost to follow-up

A total of two (4%) patients who were successfully randomised and revealed did not complete follow-up. Both patients were in the 'No FS' arm. A total of seven recruited patients did not attend their second and final follow-up appointment. Two were in the 'FS' arm and five in the 'No FS' arm. This includes two patients who were recruited but never randomised, three

patients who were randomised but never revealed and two patients who were successfully randomised and revealed but did not complete their follow-up. Overall, there was a tendency for patients in the 'No FS' arm to not complete follow-up.

7.2.1.6 Reasons for loss to follow-up

In both cases described above loss to follow-up was because the second follow-up visit did not coincide with the patient's routine clinical follow-up. Both patients were not willing to make a trial specific visit. However, they did attend their first follow-up visit. This attrition rate of patients was better than expected prior to commencement of the trial. In the vast majority of cases the second follow-up visit did coincide with the patient's routine clinical follow-up.

7.2.2 Outcomes related to trial conduct

7.2.2.1 Reasons for failure to reveal allocation

The times that allocations were revealed were cross referenced with the start and finish times of surgery. As mentioned in section 5.12.2.1, the eCRF highlighted patients who had their allocation revealed outside this time window. Only one patient had their allocation revealed before the start of surgery. This was due to the recruiting surgeon misunderstanding the protocol. A Corrective & Preventative Action (CAPA) was undertaken (see Appendix E.1 CAPA number 1).

The summary of surgical characteristics by treatment arm presented in Table 12 shows that the allocation was revealed a median of two hours after the start of surgery. The lower limit of the IQRs for either arm was not below one hour suggesting good compliance with this aspect of the protocol. Figure 24 shows a histogram of the time to revealing allocations measured in hours. As observed, there is a single patient with negative time which relates to the protocol deviation described in E.1 CAPA number 1.

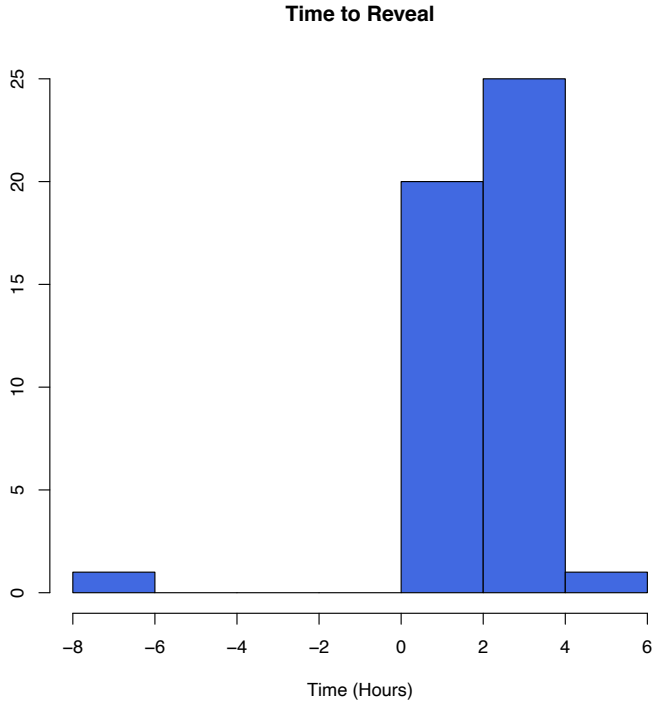


Figure 24 Histogram of length of time between start of surgery and reveal time

On a separate occasion LCTU IT staff were uncontactable within normal working hours to resolve an issue with revealing the allocation during surgery. The recruiting surgeon was unable to remember their password and reveal the allocation. This resulted in prolonging the patient's surgery. Because the issue could not be resolved in a timely fashion, the patient was empirically placed in the control arm. Coincidentally the patient had also been randomised to the control arm. A second CAPA was undertaken (see Appendix E.2 CAPA number 2).

7.2.2.2 Protocol adherence

All randomised patients underwent their allocated treatment. Only two CAPAs were undertaken throughout the entire study period (see E.1 and E.2). They can be summarised as follows:

1. A surgeon revealed the allocation prior to the start of surgery

2. A surgeon documented the use of FS in the operation note thereby unblinding the outcome assessors.
3. Trials unit IT staff were uncontactable within normal working hours to resolve an issue with revealing the allocation during surgery. This resulted in prolonging the patient's surgery.

The PI from QVH provided the following feedback on their experience of the DEFeND REPT protocol:

It was thought that the trial was labour intensive

RN support was limited and was not available throughout the entire working week. This issue made completion of eCRFs in real time (for drain volume and removal) particularly difficult. Out of hours research duties required surgical trainee involvement. The trainees were not always familiar with the study and some were not motivated to engage.

Issues with clinician engagement.

The trial required the PI to be constantly aware of potentially eligible patients and drive recruitment through his presence in the department. Surgical colleagues were not proactive recruiters and potentially eligible patients were lost if the PI was absent. As mentioned previously, some surgeons were not happy to place only one drain in the wound and did not recruit to the trial. Trainee engagement may have been related to issues with accessing trial software to complete the eCRF. Trial recruitment is also not currently a SAC requirement to progress in training. Not every clinician had a valid GCP certificate at the start of the trial.

Adherence to protocol.

Adherence to the protocol was good. There was good use of the trial protocol videos and flow charts. The PI played the videos regularly to theatre staff and surgeons to ensure adherence to the protocol. The PI suggests a quality assurance step to assess staff on their familiarity with the protocol would be beneficial.

The experience from AUH was more positive. RN support and clinician engagement was good, and the trial was delivered ahead of time and target.

7.2.2.3 Accuracy of data recording

The quality of the study data was assessed as the number of missing data points and possible outliers as well as any protocol deviations and issues with allocation concealment that were observed.

Missing Data

The distribution of missing data between treatment arms is shown in Table 15. Overall, there is an even distribution. PT and aPTT blood tests that measure the patient's clotting was missing in 33% and 35% of patients respectively. Table 16 demonstrates that QVH had a relatively higher rate of missing data, particularly in recording pre-operative blood tests. The relatively higher number of patients missing PT and aPTT may be because these blood tests are not routinely performed.

Table 15 Summary of missing data by treatment arm

	Variable	Fibrin Sealant	No Fibrin Sealant	Unassigned	Total
Baseline Demographics	**Total**	**26**	**25**	**2**	**53**
	Hb	3 (12%)	2 (8%)	0 (0%)	5 (10%)
	Platelets	3 (12%)	2 (8%)	0 (0%)	5 (10%)
	White cells	3 (12%)	3 (12%)	0 (0%)	6 (12%)
	PT	9 (35%)	8 (32%)	1 (50%)	17 (33%)
	aPTT	10 (38%)	8 (32%)	1 (50%)	18 (35%)
	Total	**25**	**23**		**48**
Drain	Drain volume	0 (0%)	1 (4%)	-	1 (2%)
NDII	Follow-up 2	1 (4%)	3 (13%)	-	4 (8%)
Surgery	Cutting Instrument	0 (0%)	1 (4%)	-	1 (2%)
	Blood Loss	0 (0%)	1 (4%)	-	1 (2%)
	Length of Surgery	2 (8%)	3 (13%)	-	5 (10%)
	Time to Reveal	0 (0%)	2 (9%)	-	2 (4%)
	Time to Recovery Room	2 (8%)	2 (9%)	-	4 (8%)

Table 16 Summary of missing data by site

	Variable	Queen Victoria Hospital	Aintree University Hospital	Total
Baseline Demographics	**Total**	**7**	**46**	**53**
	Hb	2 (29%)	3 (7%)	5 (10%)
	Platelets	2 (29%)	3 (7%)	5 (10%)
	White cells	3 (43%)	3 (7%)	6 (12%)
	PT	7 (100%)	11 (24%)	18 (33%)
	aPTT	7 (100%)	12 (26%)	19 (35%)
	Total	**6**	**42**	**48**
Drain	Drain volume	0 (0%)	1 (2%)	1 (2%)
NDII	Follow-up 2	1 (17%)	3 (7%)	4 (8%)
Surgery	Cutting Instrument	0 (0%)	1 (2%)	1 (2%)
	Blood Loss	0 (0%)	1 (2%)	1 (2%)
	Length of Surgery	1 (17%)	4 (10%)	5 (10%)
	Time to Reveal	0 (0%)	2 (5%)	2 (4%)

Possible Outliers

The summary of possible outliers presented in Table 17 demonstrates there was good balance of outliers between treatment arms with the majority categorised as 'mild'. The main difference of note is that the two 'severe' outliers for blood loss were both in the 'FS' arm. Because increased intra-operative blood loss if often associated with difficult or complicated surgery, this favours the 'No FS' arm. This will be somewhat neutralised by the fact that there were four 'mild' outliers for blood loss in the 'No FS' arm compared to two in the 'FS' arm.

Table 17 Summary of possible outliers by treatment arm

	Covariate	Severity	Fibrin Sealant	No Fibrin Sealant	Total
	Total		25	23	48
Drain	Volume	Mild	0 (0%)	1 (4%)	1 (2%)
Surgical Outcomes	Blood Loss	Mild	2 (8%)	4 (17%)	6 (13%)
		Severe	2 (8%)	0 (0%)	2 (4%)
	Length of Surgery	Mild	0 (0%)	1 (4%)	1 (2%)
		Severe	1 (4%)	0 (0%)	1 (2%)
	Time to Reveal	Mild	0 (0%)	1 (4%)	1 (2%)
		Severe	0 (0%)	1 (4%)	1 (2%)

7.2.3 Fidelity of the blinding process

The Bang Blinding Index (BBI) (173) for allocation concealment was performed by asking patients, research nurses and surgeons to predict which treatment arm patients were allocated to.

7.2.3.1 Fidelity of blinding patients

The responses patients gave when asked to guess their treatment allocation is provided in Table 18. Whilst 15/24 patients managed to correctly predict they received FS, 10/21 patients in the 'No FS' arm incorrectly thought they received FS. Overall, there was a tendency for patients to believe they received the intervention (whether they truly did or not). The BI and associated 95% CI for the FS arm indicates a tendency towards unblinding. The BI and associated 95% CI for the 'No FS' arm indicates a tendency towards 'negative guessing'. Overall, there is a tendency towards the 'wishful thinking' phenomenon which suggests blinding has been effective.

Table 18 Fidelity of the blinding process for patients.

	Strongly Believe they received Fibrin sealant	Somewhat believe they received Fibrin sealant	Somewhat believe they did NOT receive Fibrin sealant	Strongly believe they did NOT receive Fibrin sealant	Don't know
Fibrin Sealant	10	5	2	2	5
No Fibrin Sealant	6	4	0	2	9

Bang index of FS arm: 0.43 (V = 0.02, 95% CI 0.29 – 0.57)

Bang index of No FS arm: -0.36 (V = 0.02, 95% CI 0.22 – 0.50)

(V = variance estimate, CI = confidence interval)

7.2.3.2 Fidelity of blinding Research Nurses

The responses RNs gave when asked to guess the patient's treatment allocation is provided in Table 19. Whilst RNs managed to correctly predict the patient received FS in 19/24 occasions, they also incorrectly thought the patient received the FS on 16/21 occasions. Overall, there is a tendency for RNs to believe the patients received the intervention (whether they truly did or not). The BI and associated 95% CI for the FS arm indicates a tendency towards unblinding. The BI and associated 95% CI for the 'No FS' arm indicates a tendency towards negative guessing. Again, there is an overall tendency towards the 'wishful thinking' phenomenon which suggests blinding has been effective.

Table 19 Fidelity of the blinding process for Research Nurses.

	Strongly Believe they received Fibrin sealant	Somewhat believe they received Fibrin sealant	Somewhat believe they did NOT receive Fibrin sealant	Strongly believe they did NOT receive Fibrin sealant	Don't know
Fibrin Sealant	7	12	4	0	1
No Fibrin Sealant	5	11	5	0	0

Bang index FS arm: 0.47 (V = 0.01, 95% CI = 0.37 – 0.57)

Bang index No FS arm: -0.38 (V = 0.02, 95% CI = -0.52 – -0.24)

(V = variance estimate, CI = confidence interval)

7.2.3.3 Fidelity of blinding surgeons

The responses surgeons gave when asked to guess the patient's treatment allocation is provided in Table 20. Most surgeons reported not knowing what treatment patients received and did not attempt a random guess. The BI and associated 95% CI for the FS arm indicates a tendency towards unblinding. The BI and associated 95% CI for the 'No FS' arm indicates successful blinding.

Table 20 Fidelity of the blinding process for surgeons.

	Strongly Believe they received Fibrin sealant	Somewhat believe they received Fibrin sealant	Somewhat believe they did NOT receive Fibrin sealant	Strongly believe they did NOT receive Fibrin sealant	Don't know
Fibrin Sealant	2	2	1	0	19
No Fibrin Sealant	0	2	1	1	15

Bang index FS arm: 0.22 (V = 0.01, 95% CI = 0.12 – 0.32)

Bang index No FS arm: -0.03 (V = 0.02, 95% CI = -0.17 – 0.11)

(V = variance estimate, CI = confidence interval)

7.2.4 Determining the minimal clinically important differenc

The participant responses regarding clinical endpoints and MCID were summarised in the End of Trial eCRF by investigators. Responses from 42 patients (no response recorded for six patients) are shown in Table 21. These responses have been unmodified from the way the

investigator recorded them. Table 21 also demonstrates the assignment of codes for each response and the overarching theme(s). The visual mapping used to explore the relationship between codes and themes is shown in Figure 25.

7.2.4.1 Assignment of codes

An explanation and context for each code is provided below. The term 'response' is used to describe all the words entered within the eCRF. The term 'comment' is used to describe parts of the 'response' that are relevant to the research question.

- **"Reducing length of stay"**. This was the most frequently applied code and demonstrated that many patients considered timely discharge an important priority. The code was assigned to comments made in different contexts. This included: comments that conveyed a wish to minimise the consumption of finite resources; comments that described a dislike for hospital environments; comments that conveyed a wish to heal and recover quickly. This demonstrated that participants recognised a health economic benefit to their improved recovery and timely discharge.

- **"Speed of healing"**. This was a frequently assigned code that was applied to comments that conveyed the importance of quick wound healing. This code was often associated with responses that also included codes for "quicker recovery", "less complications" and "reducing length of stay". The code was often associated with responses that conveyed a patient's wish to get back to normal as quickly as possible after surgery.

- **"Less complications"**. This code was assigned to comments that were made in different contexts (similar to "reducing length of stay"). This included: comments that conveyed a wish to optimise wound healing through the avoidance of complications; comments that conveyed a wish to reduce the consumption of hospital resources through the avoidance of complications. This suggests that many participants recognised that

complications were not only associated with poor healing but also associated with an increased drain on finite resources.

- **"Better healing"**. This code was applied to comments that prioritised wound healing in a broader sense and focused on the quality (rather than speed) of wound healing. It was associated with responses that also included codes for "less complications", "quicker recovery" and "reduction of pain".

- **"Quicker recovery"**. This code was applied to comments that viewed healing in a more holistic manner. This included comments that considered energy levels, physical function and psychosocial well-being. Conversely, "speed of healing" was associated with comments that focused specifically on healing of the surgical site.

- **"Reduction in pain"**. This was a relatively infrequently applied code that was associated with responses that also contained codes for "better healing", "less complications" and "easier to manage wound". It appears to reflect a belief that a wound that is less painful is also less likely to be associated with complications or impaired healing.

- **"Reducing hospital costs"**. This code was applied to comments where the patient recognised that their care incurred a financial cost to the NHS, and they considered reducing this cost a priority. This code was associated with responses that also contained codes for "less complications", "reducing length of stay" and "need for less medication". This suggests that some patients wished to reduce the financial cost of their care so that more finances were available for other healthcare users.

- **"Easier to manage wound"**. This code was only applied once and was associated with a response that also included a code for "reduction in pain".

- **"Need for less medication"**. This code was used only once and associated with a response that also included a code for "reducing hospital costs".

7.2.4.2 Development of themes

Through the analysis of codes and patient responses two dominant overarching themes were developed.

- **Improved wound healing and recovery from surgery**. An overarching theme that described the patient's priority to undergo surgery with as little impact on their physical function and day-to-day life as possible. Patients wanted their wounds to heal as quickly and as painlessly as possible without complications. Some patients recognised that their improved wound healing would also have health economic benefits through the consumption of less resources.

- **Less use of hospital resources**. An overarching theme that described the patient's priority to not utilise excessive hospital resources. This sentiment sometimes originated from an altruistic sense of not burdening the NHS and thinking about the impact of their own care on other healthcare users. However, for some patients this sentiment originated from a dislike of hospital environments and wanting to get home as soon as possible. Many patients recognized a connection between improved wound healing and the consumption of less resources. Consideration was given to whether "less use of hospital resources" was in fact a sub-theme of "improved wound healing and recovery from surgery". However, the sub-optimal qualitative methodology and brevity of recorded patient responses meant that this could not be explored further. Many responses were assigned a single code for "reducing length of stay" and the context in which these responses were made was unknown.

Table 21 Raw data demonstrating the thematic analysis of patient responses to the MCID question. The table also demonstrates how comments were assigned codes that were developed into two central themes. (MCID = Minimal Clinically Important Difference).

Response	Codes	Themes
No infection, shorter stay in hospital, no bleeding or seepage from the wound	Less complications; reducing length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Speed of healing is an important priority as well as experiencing less pain. Reduction in healing time by 50%	Speed of healing; reduction in pain	Improved wound healing and recovery from surgery
Being in hospital the least amount of time. That would save on hospital fee and staffing etc	Reducing length of stay; reducing hospital costs	Less use of hospital resources
Speed of recovery and quicker healing. Quicker healing of scar and wound	Speed of healing; quicker recovery	Improved wound healing and recovery from surgery
Reduction of hospital stay by at least 1 day	Reducing length of stay	Less use of hospital resources
Length of stay. As retied T&O surgeon patient feels that if glue reduces cost then beneficial	Reducing length of stay; reducing hospital costs	Less use of hospital resources
Priority was less time in hospital and quick discharge. If reduces LOS by one day it would be worthwhile	Reducing length of stay	Less use of hospital resources

Response	Codes	Themes
Speed of healing. If it makes a difference the speed of healing is probably the most important	Speed of healing	Improved wound healing and recovery from surgery
Saves money. Reducing length of stay by 1 day. Going back to normality quicker. Getting out and about and having energy to go for a walk.	Reducing hospital costs; reducing length of stay; Quicker recovery	Less use of hospital resources Improved wound healing and recovery from surgery
Better healing, less infection	Better healing; less complications	Improved wound healing and recovery from surgery
Speed of healing, quicker discharge. Scar settled well. If wound heals 2-3 days quicker that would be signifi-cant. Coming out of hospital sooner is also important	Speed of healing; reducing length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Hate being in hospital. Reduce hospital stay even if only one day	Reducing length of stay	Less use of hospital resources
Faster overall healing – I would like overall healing in 3-4 weeks	Speed of healing	Improved wound healing and recovery from surgery
Scar healing and help recovery	Better healing; quicker recovery	Improved wound healing and recovery from surgery
Cause less pain and easier to remove staples	Reduction in pain; easier to manage wound	Improved wound healing and recovery from surgery

Response	Codes	Themes
Reduction in pain and infection through improved healing	Better healing; less complications; reduction in pain	Improved wound healing and recovery from surgery
Reduction in length of stay- discharge day after surgery	Reduced length of stay	Less use of hospital resources
Less time in hospital the better- I would want this to reduce LOS by at least 1 day	Reduced length of stay	Less use of hospital resources
Wound healing leading to hospital stay reduction by at least one day	Speed of healing; Reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Reduction in hospital stay and saving money for the hospital and benefitting patients. I would like this to be that you are discharged at least the day after surgery.	Reduced length of stay; reducing hospital costs	Less use of hospital resources
Early discharge – the day after surgery	Reduced length of stay	Less use of hospital resources
Surgical assistance leading to effective wound healing and subsequent reduction in LOS. I would want that to be the same as my hospital stay- 2days	Better wound healing; easier to manage wound; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Home one day earlier	Reduced length of stay	Less use of hospital resources

Response	Codes	Themes
Recovery period as short as possible, quick healing. Back to normal as soon as possible	Speed of healing; quicker recovery	Improved wound healing and recovery from surgery
Reduction in complications, pain and hospital stay	Less complications; reduction in pain, reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Improvement in speedy recovery – early discharge by at least 1 day	Quicker recovery; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Successful healing, obviously no infection and quicker discharge by as much as is practical	Better healing; less complications; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Less time in hospital	Reduced length of stay	Less use of hospital resources
Reduction in aftereffects; improved healing for patients and therefore saving the hospital money with earlier discharge	Better healing; less complications; reducing hospital costs; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Preventing infection	Less complications	Improved wound healing and recovery from surgery

Response	Codes	Themes
Substantial benefits over traditional ways- with significant quicker healing of the wound with faster discharge and less returns to hospital with wound issues	Speed of healing; less complications; reduced length of stay; reducing hospital costs	Improved wound healing and recovery from surgery Less use of hospital resources
Reduces inpatient time by at least one night, reduces re-admissions for wound problems and speeds up the healing process to avoid infection	Reduced length of stay; less complications; speed of healing	Less use of hospital resources Improved wound healing and recovery from surgery
Reduction in pain and speedy healing effects would make it a worthwhile expense	Reduction in pain; speed of healing	Improved wound healing and recovery from surgery
Reducing aftercare – time spent in hospital and healing potential to be maximised	Reduced length of stay; reducing hospital costs, better healing	Improved wound healing and recovery from surgery Less use of hospital resources
Faster recovery- eating and drinking sooner. Earlier discharge – hospital stay at least halved	Quicker recovery; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Speedier recovery and quicker discharge from hospital- not really able to quantify how much quicker	Quicker recovery; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources

Response	Codes	Themes
Faster recovery- less time spent in hospital. Less medication – more money saved by the hospital	Quicker recovery; reduced length of stay; reducing hospital costs; need for less medication	Improved wound healing and recovery from surgery Less use of hospital resources
Earlier discharge from hospital	Reduced length of stay	Less use of hospital resources
Quicker turnaround for healing process – less resources used from the hospital	Speed of healing; reducing hospital costs	Improved wound healing and recovery from surgery Less use of hospital resources
I want to see a good healing process with less swelling. No complications to reduce hospital resources and length of stay	Better healing; less complications; reducing hospital costs; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Improvement in post-operative condition, general well-being leading to an earlier discharge	Better healing; quicker recovery; reduced length of stay	Improved wound healing and recovery from surgery Less use of hospital resources
Heal up as quickly as possible	Speed of healing	Improved wound healing and recovery from surgery

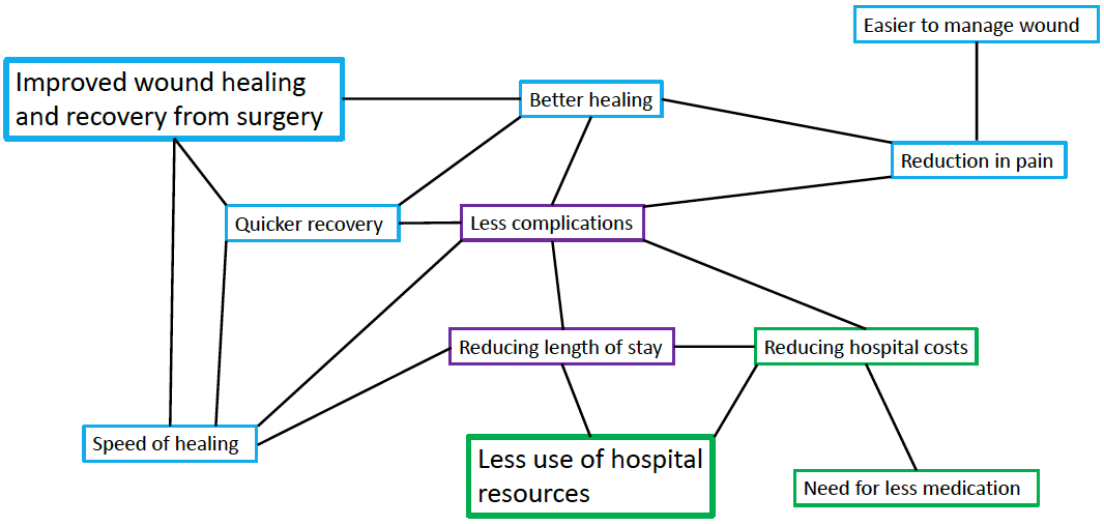


Figure 25 Visual mapping was used to explore the relationship between codes and themes. The themes are in larger boxes corresponding to the colour of their codes. Codes in blue boxes relate to the "improved wound healing and recovery from surgery" theme. Codes in green boxes relate tot he "less use of hospital resources" theme. Codes in purple boxes are translational codes that relate to both themes.

The visual mapping in Figure 25 shows a complex interconnected framework that attempts to describe how patients responded to the research question. Even though the two dominant themes were not directly connected to one another, they were connected indirectly through the transitional codes "less complications" and "reducing length of stay" (purple boxes). This implies that many patients recognised that complications were not only associated with poor healing but also associated with increased length of stay. They also recognised that there was a health economic benefit to their improved healing and timely discharge.

The most frequently applied code was "reducing length of stay" and in many cases was the only code applied to a response. This means that many patients considered timely discharge an important priority. However, the use of a poorly conceived qualitative methodology meant the context in which several responses were made is unknown. Without exploring the context, it is unclear whether patients considered it a priority from a health economic, avoidance of hospital environments or improved healing perspective.

7.2.5 Relevance of learning curve

Surgeons were classified as being either 'experienced' or 'inexperienced' in using FS in ND according to the criteria discussed in section 5.12.5.2. The performance proxies used to investigate the presence of a learning effect were surgical complications using the CCI and drainage volume (ml). To account for the theory that the anatomy of level I is less conducive to the adhesive effects of FS (as described in section 5.12.5.2), a comparison between NDs involving level I and NDs not involving level I was also made.

The mean CCI by surgeon experience is demonstrated in Table 22. The mean rather than the median CCI was chosen because many patients who did not suffered any complication had a CCI of 0. In most circumstances the median CCI was 0 and therefore not a useful discriminator. This table demonstrates that FS reduced the mean CCI when used by experienced surgeons. However, the mean CCI in the FS arm was comparable to the No FS arm when FS was used by inexperienced surgeons. Equally, in the No FS arm the difference between inexperienced and experienced surgeon was comparable.

Table 22 Mean Comprehensive Complication Index (CCI) by treatment arm and surgeon experience

Treatment Arm	Inexperienced Surgeons	Experienced Surgeons
Fibrin Sealant	10.7	4.5
No Fibrin Sealant	8.8	10.9

The CCI by dissection level is demonstrated in Table 23. This table demonstrates that when FS was used in NDs that included level I, it was associated with an increase in mean CCI. However, when FS was used in NDs that did not include level I, it was associated with a

decrease in mean CCI. In the No FS arm the difference between a ND including level I and not including level I was comparable.

Table 23 Mean Comprehensive Complication Index (CCI) by treatment arm and inclusion of Level 1 in neck dissection.

Treatment Arm	Not Level I	Level I
Fibrin Sealant	2.6	22.4
No Fibrin Sealant	11.2	7.0

In the FS arm there was a notable difference in mean CCI between experienced and inexperienced surgeons. The presence of a learning effect may be one explanation for this difference. However, there was also a notable difference in the FS arm between NDs including level I and not including level I. Out of the 19 NDs performed by inexperienced surgeons, 10 included level I. Out of the 29 NDs performed by experienced surgeons, only 2 included level I. Because inexperienced surgeons performed more NDs that included level I, it is not clear whether the increased mean CCI was associated with a learning effect or the type of ND.

The median total drain volume (ml) by surgeon experience is demonstrated in Table 24. This table demonstrates that when experienced surgeons used FS the median total drain volume between treatment arms was comparable. However, when the FS was used by inexperienced surgeons the drain volume was higher in the FS arm.

Table 24 Mean total drain volume (ml) by treatment arm and surgeon experience.

Treatment Arm	Inexperienced Surgeons (ml)	Experienced Surgeons (ml)
Fibrin Sealant	189.5	60
No Fibrin Sealant	88.5	67

The median total drain volume (ml) by dissection level is demonstrated in Table 25. This table demonstrates that in the FS arm dissection of level I was associated with a higher median drain volume. However, in the No FS arm the median drain volumes were the same. It also demonstrates that when level I was dissected, the use of FS was associated with a higher median drain volume.

Table 25 Mean total drainage volume (ml) by treatment arm and inclusion of Level 1 in neck dissection

Treatment Arm	Not Level I	Level I
Fibrin Sealant	67	108.5
No Fibrin Sealant	79	79

7.2.6 Safety

No SAEs or SUSARs were reported during the study. No patients needed to be unblinded.

7.3 Clinical Outcomes

7.3.1 Clavien-Dindo classification of surgical complications

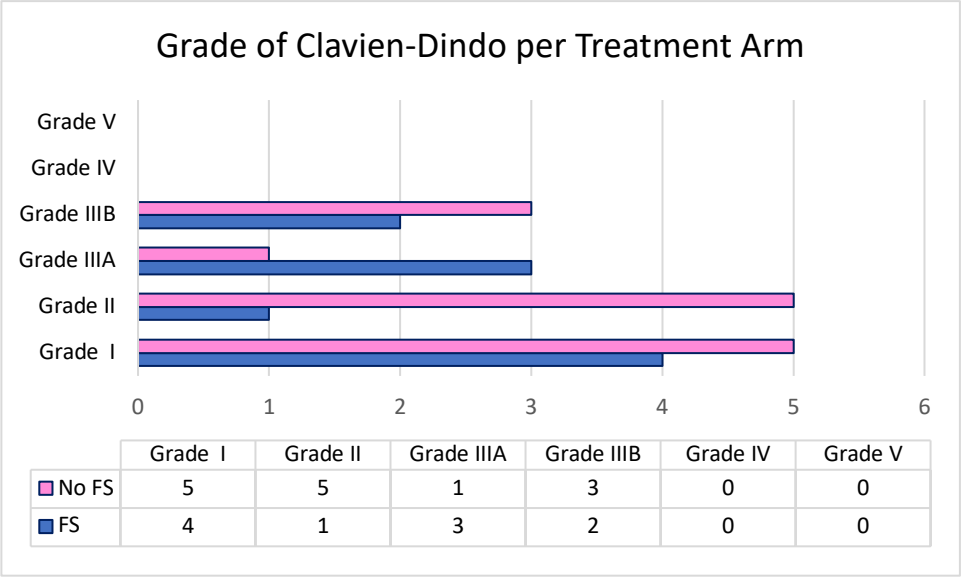
Details of complications according to number and severity for each treatment arm is provided in Table 26. In total, 16 (33.3%) patients experienced at least one event. Overall, there were more complications in the 'No FS' arm (14 complications in 'No FS' arm 10 complications in 'FS' arm). The numbers of neck SSI, wound breakdown and seroma were similar across both arms. There were more haematomas that required a return to theatre in the 'No FS' arm. 'Other Complications' in the 'FS' arm included a patient who bled from their oropharynx resection site that returned to theatre for haemostasis (grade IIIB) and a patient who pulled their drain out too

early (grade I) with no other sequelae. The oropharynx bleed was not directly related to the use of FS in the ND wound. Pulling the drain out too early is not a complication in the true sense but was reported as such by investigators at site. In the 'No FS' arm 'Other Complications' included: a patient who suffered a transient ischaemic attack (TIA) and started on antiplatelet therapy (grade II); a patient who suffered 'Horner's Syndrome' secondary to ND but did not require any treatment (grade I); a patient who had leakage of serous fluid from their drain site (after the drain was removed) but did not require any treatment (grade I).

Table 26 Description of complications and Clavien-Dindo grade by treatment arm

Complication	Fibrin Sealant		No Fibrin Sealant	
	Number	Grade	Number	Grade
Neck SSI	1	IIIA	1	II
Other SSI	0		2	II, II
Neck Haematoma	1	IIIB	3	IIIB, IIIB, IIIB
Wound Breakdown	1	I	1	I
Seroma	4	I, I, IIIA, IIIA	3	I, I, IIIA
Chest Infection	1	II	1	II
Other Complications	2	I, IIIB	3	I, I, II
Total	**10**		**14**	

A description of the distribution of complications according to treatment arm and Clavien-Dindo grade is rovided in Figure 26. It shows that there are more complications in the 'No FS' arm for every grade apart from IIIA. From this data it appears as though FS was not protective against seroma formation.



	Grade I	Grade II	Grade IIIA	Grade IIIB	Grade IV	Grade V
No FS	5	5	1	3	0	0
FS	4	1	3	2	0	0

Figure 26 Bar chart describing distribution of complications by Clavien-Dindo grade and treatment arm

The 24 complications reported in this study were distributed between 16 patients indicating that some patients experienced more than one complication. The CCI uses an algorithm to calculate a patient's overall morbidity using the Clavien-Dindo grade and provides a score between 0 – 100. The algorithm takes account of patients who experience multiple complications and increases their score accordingly. Table 27 demonstrates the mean and median CCI score for each arm. The 'FS' arm had a lower mean CCI score than the 'No FS' arm. Whilst the median CCI was 0 for both arms, the upper limit of the IQR was higher in the 'No FS' arm. These values in combination with the descriptive data in Table 26 and Figure 26 signal that FS may reduce the number and severity of complications. This was a REPT and not powered to detect a difference between treatment arms. Therefore unsurprisingly, the comparisons between treatment arms using the T-test and Chi-square test were not statistically significant.

Because none of the complications reported were Clavien-Dindo grade IV or above no SAEs were reported. No patient suffered a severe hypersensitivity reaction, air embolism or new

diagnosis of a blood borne infection. Therefore, no patients needed to be unblinded through the course of the trial.

Table 27 Description of mean and median Comprehensive Complication Index (CCI) across treatment arms.

	Fibrin Sealant	No Fibrin Sealant	Total	P-value
Mean (SD)	6.5 (12.8)	9.9 (14.2)	8.1 (13.5)	0.3875 (T-test)
Median (IQR)	0 (0, 6.5)	0 (0, 20.9)		0.4481 (T-test) 0.6917 (Chi-Square test)

SD = standard deviation, IQR = interquartile range

7.3.2 Total wound drainage volume

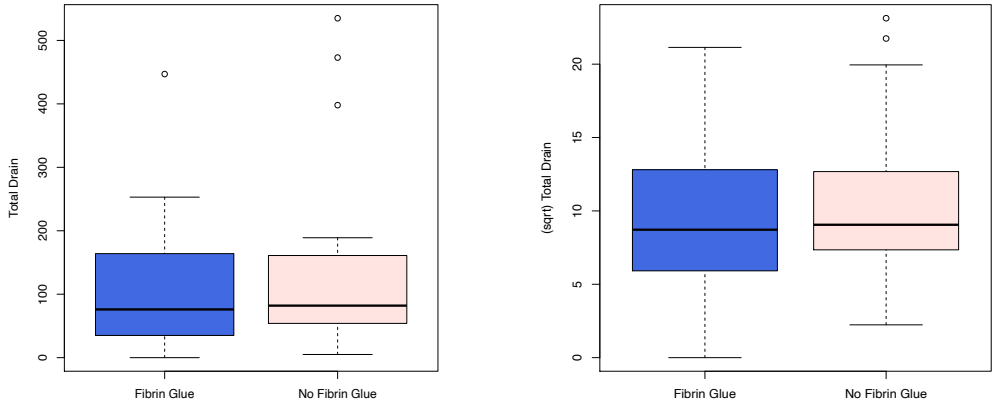
The summary (median [IQR]) of drain volumes on the natural and square root scales are shown in Table 28. The median total wound drainage was lower in the 'FS' arm. A comparison between treatment groups is performed using a T-test was not statistically significant (p=0.482). Again, this study was not designed or powered to detect a difference.

Table 28 Total wound drainage volume (ml) by treatment arm.

Outcome	Fibrin Sealant	No Fibrin Sealant
Natural Scale	76 (35, 164)	82 (54, 161)
Sqrt Scale	8.718 (5.916, 12.806)	9.055 (7.347, 12.68)
T-test (sqrt scale)		T=-0.709 [P =0.482]

Sqrt = square root

Boxplots for total drain volume by treatment arm on a natural and square root scale are shown in Figure 27. They demonstrate that volumes were very similar. However, the IQR was wider for the 'FS' arm.



A **B**

Figure 27 Boxplots showing the total drain volume (ml) by treatment arm measured on the natural (A) and square root (B) scale.

7.3.3 Drain outcomes

The median (IQR) values for 'time to threshold', 'time to drain removal' and 'length of stay' by treatment arm are shown in Table 29. Overall, there is signal that FS may reduce 'time to drain removal' and 'length of stay'. P-values do not indicate a statistically significant difference however, as mentioned previously, this study was not designed or powered to detect a difference.

Table 29 Median time to threshold, time to drain removal and length of stay (days) by treatment arm.

Outcome	Fibrin Sealant	No Fibrin Sealant	P-value
Time to Threshold	2.637 (2.625, 3.625)	2.625 (2.62, 3.628)	0.642
Time to Drain Removal	2.667 (2.417, 3.576)	3.399 (2.5, 4.266)	0.503
Length of Stay	3.476 (2.635, 4.541)	3.735 (3.106, 4.616)	0.479

7.3.3.1 Time to threshold

The drain was removed once the rate of drainage reached below the threshold of 1.25ml/hr as described in the drain removal algorithm in Figure 15. Table 29 demonstrates that the median (IQR) time in days it took to reach this threshold was approximately 2.6 days for both arms.

7.3.3.2 Time to drain removal

Patients in the 'FS' arm had a median (IQR) time to drain removal in days that was lower than patients in the 'No FS' arm (2.667 days in the FS arm and 3.399 days in the No FS arm).

7.3.3.3 Length of stay

Patients in the 'FS' arm had a median (IQR) length of stay in days that was slightly lower than patients in the 'No FS' arm (3.476 days in the FS arm and 3.735 days in the No FS arm).

7.4 Patient Reported Outcomes

7.4.1 Neck Dissection Impairment Index

NDII values were collected on 53 patients at baseline and 48 patients at follow-up. Table 30 summarises the median (IQR) NDII scores for baseline and follow-up by treatment arm. It shows that the baseline NDII was the same but patients in the 'FS' arm had a lower median NDII at follow-up. A lower score is associated with better function and HRQoL.

Table 30 Median Neck Dissection Impairment Index (NDII) at baseline and follow-up by treatment arm.

	Fibrin Sealant	No Fibrin Sealant
Baseline	11 (10, 13)	11 (10, 12)
Follow-Up	16.5 (13.75, 22.25)	20 (14, 22)

	Fibrin Sealant	No Fibrin Sealant
Difference	4.5 (0, 11.5)	7 (2, 11)

7.4.2 Neck pain scale

The median (IQR) pain VAS that was observed over the duration of the study by treatment arm is provided in Table 31. It shows that pain VAS was low for all patients and very similar across both treatment arms.

Table 31 Median Neck Pain Scale at baseline and follow-up by treatment arm.

	Fibrin Sealant	No Fibrin Sealant	Overall
Baseline	0 (0, 1)	0 (0, 1)	0 (0, 1)
Follow-up 1	1 (0, 2)	1 (0, 3)	1 (0, 3)
Follow-up 2	1 (0.75, 2)	1 (0, 2)	1 (0, 2)

The mean pain VAS across treatment arms is provided in Figure 28. The blue line represents patients in the 'FS' arm and the red line represents patients in the 'No FS' arm. The figure shows that the pain VAS was slightly lower in the 'No FS' group but the standard error of the means (SEM) overlapped suggesting no significant difference.

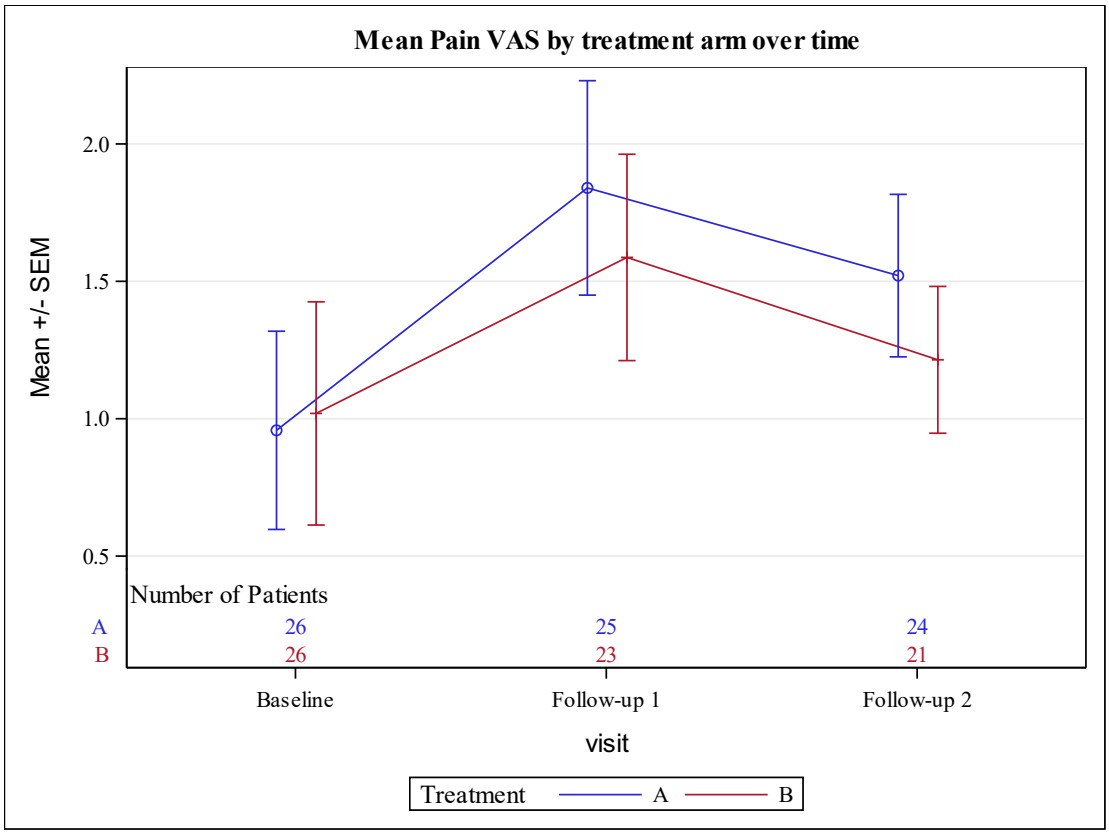


Figure 28 Profile plot to show the change in Neck Pain Scale over the study duration by treatment arm. Blue line represents interventional arm. Red line represents control arm.

7.4.3 Wound Healing Questionnaire

The median (IQR) of WHQ between treatment arms is provided in Table 32. Overall patients in the 'FS' arm had a lower WHQ score than patients in the 'No FS' arm. A lower median WHQ score is associated with a lower rate of SSI and corresponds well to the findings in Table 26. As with previous clinical outcomes, the study was not powered to detect a difference and the p value is not significant.

Table 32 Median Wound Healing Questionnaire (WHQ) score by treatment arm.

Fibrin Sealant	No Fibrin Sealant	Total	T test
2 (1, 5)	4 (0, 5)	3 (1, 5)	T=-0.709 [P =0.482]

The WHQ has been validated in patients undergoing abdominal surgery but not in HNS.(149) It was felt important to include this instrument in the DEFeND REPT to understand how it can be applied to HNS trials. If the WHQ was successfully deployed, a strong argument could be made for the development of a similarly designed HNS specific instrument.

The permission from colleagues at the University of Bristol to use the WHQ in DEFeND was dependent on providing them with anonymized and contemporaneous data on WHQ as well as the clinician diagnosed validation. As previously mentioned, there was no intention to use the small sample size of the DEFeND REPT to formal validate the WHQ in HNS. However, it was thought that the data being collected may provide some insight into how successfully the WHQ was deployed.

The box plot for WHQ score according to a diagnosis of SSI is shown in Figure 29A. It demonstrates that a higher WHQ was indeed associated with a diagnosis of SSI. The ROC curve which demonstrates an AUC of 0.95 is shown in Figure 29B. This indicates that the WHQ was a very good discriminator between HNS patients who had SSI and those that did not. A WHQ score of 5 was the most sensitive cut-off with a sensitivity of 1.0 and specificity of 0.76. A WHQ score of 14 was the most specific cut-off with a sensitivity of 0.75 and specificity of 1.0. These results correlated well with the Bluebelle validation study that produced an AUC of 0.91 and a cut-off between 6 – 8.(149)

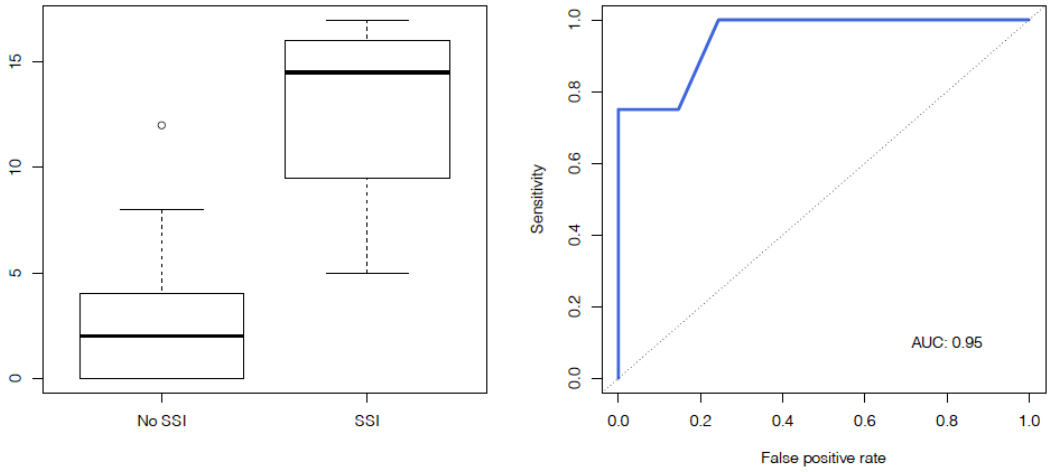


Figure 29 A: Box plot demonstrating median Wound Healing Questionnaire (WHQ) score by clinician diagnosis of SSI. B: Receiver Operating Characteristic curve demonstrating performance of WHQ as a test for SSI in HNS patients

Chapter 8. DISCUSSION

8.1 Summary of the Work

8.1.1 Distribution of baseline and surgical characteristics

The even distribution of variables across both treatment arms is supportive of effective an randomization strategy, however, some differences between treatment arms were noted. Patients in the FS arm had better performance status (PS) and all patients who had modified radical NDs were in the 'No FS' arm. These findings suggest that patients in the FS arm tended to have an improved premorbid physiological state and/or that they received less extensive NDs. However, in contradiction to this, nodal yield was very similar across both treatment arms and patients in the 'No FS' arm had less intra-operative blood loss. Randomisation was only stratified by site; therefore, differences would not be unexpected in a study with a small sample size. In summary, randomisation has been effective and if this strategy was employed in a larger definitive trial, it is expected that the differences would be inconsequential to the outcome.

8.1.2 Recruitment & retention Outcomes

8.1.2.1 Screening and recruitment

The overall recruitment rate for the study was 5.3 patients/month (4.6 patients/month for AUH and 1.4 patients/month for QVH). The overall recruitment rate was higher than the predicted four patients/month. This prediction was based on 30% of 180 eligible patients being recruited over 12-months. The study saw a higher proportion of patients being recruited from a smaller pool of eligible patients. The net effect being that the recruitment target of 50 patients was reached two months ahead of schedule.

Whilst the overall profile of recruitment was a positive finding, there was considerable disparity between AUH and QVH. AUH outperformed QVH which was unable to achieve their target of two patients per month. A total of 22 potentially eligible patients underwent surgery at QVH during the study period but only nine were screened. To some extent this disparity was expected and was the reason why QVH was chosen as a site. As a pragmatic design is being proposed for the definitive trial, it was important to evaluate the performance of a non-academic centre. It was thought that AUH performed well because it has a strong track record of recruiting well to head and neck trials. The surgeons were therefore familiar with the research process and recruiting patients to trials. Furthermore, several surgeons were advocates of using FS in ND and keen to engage in the trial. This is evidenced by their publication of two retrospective studies on the subject. (101, 103) AUH is also endowed with a dedicated team of RNs who can harmonise the screening and recruitment process into daily practice.

Conversely QVH faced several challenges and obstructions to explain why they may have struggled more with recruitment. Firstly, the green light process and trial opening took longer than expected because the Research & Development department had little experience of opening trials and were naturally cautious. This resulted in a narrowed window for recruitment. As a result, a decision was taken to not open spoke sites (see sections 4.4.2 and 7.2.1.4 for further details). At the time It was felt that opening spoke sites would narrow their recruitment window even further and be detrimental to their overall ability to recruit enough patients. However, the decision to press on with recruitment may have hindered their ability to recruit efficiently. It was normal practice for QVH to invite patients to a clinic one week ahead of their surgery to obtain informed consent. It was felt that this appointment would provide an ideal opportunity to take informed consent for DEFeND also. However, by not opening spoke sites, patients were not approached and given the PIS before this appointment. Despite the REC waiving the need for a 24-hour cool-off period for taking consent (see section 5.6), the issue with spoke sites may have created an avoidable barrier to recruitment. After recruitment was completed, it was realised that the trade-off between maximising the recruitment window and optimising recruitment efficiency by opening spoke sites was false. Opening spoke sites as a Patient Identification

Centres (PIC) was not considered. Opening spoke sites as PICs is far easier and less time consuming than opening them formally. This would have allowed patients to have been screened and given the PIS at spoke sites before they attended QVH. In retrospect this was an oversight and utilisation of PICs would have solved the issue previously described.

QVH surgeons were unfamiliar with the research process. This unfamiliarity with discussing clinical trials with patients and conveying equipoise as well as the perception that involvement is onerous is a systemic issue with recruitment to surgical trials. (124) Two of the seven surgeons had fundamental issues with the trial protocol e.g. they were unhappy to change their practice and use one drain instead of two on trial patients. They cited medicolegal reasons as to why this was an insurmountable issue for them. Provided the protocol and GCP guidance is followed carefully, any medicolegal claims are very unlikely to attribute blame on the surgeon. Upon reflection this may have been a symptom of their unfamiliarity with the research process and a lack of necessary research infrastructure. If efforts are not made to integrate research with routine clinical practice, it will be labour intensive and inefficient.(219) Supporting the development of a culture of research is fundamental to improving recruitment to clinical trials and RN support is a key element. The RNs at QVH worked on a part-time basis and did not provide complete cover across the working week. This meant that clinicians who were unfamiliar with the research process were required to actively engage in the research process. One of the most challenging aspects of the trial design that QVH reported was the need for real-time data entry into the eCRF. It is the role of the local CRN to support research activity at sites. Due to limited resources, it is up to sites to negotiate the type of support required. Ultimately if a site is motivated to recruit to portfolio trials, support from the local CRN should be forthcoming.

In summary, overall recruitment and specifically recruitment at AUH exceeded expectations. QVH did not perform as well as AUH due to a combination of reasons. The lack of research culture and infrastructure is not unique to QVH and needs to be factored into any future pragmatic trial design. The recruitment capabilities of QVH may have been inhibited by not using spoke sites as PICs. At the time of opening, investigators were not aware of PICs and a

decision not to open spoke sites was made under false pretenses. As a result, QVH's true recruiting potential may not have been realised. Selection of a more research capable second site may have yielded better recruitment figures. However, this approach may not have provided the same insights in terms of potential barriers to recruitment in a definitive multi-centre trial.

8.1.2.2 Reasons for failure to randomise

Approximately 20% of patients declined to participate in the study and this value was consistent across both sites. Five potentially eligible patients were not randomised because of a failure to use spoke sites as PICs. However as already discussed, QVH failed to screen thirteen potentially eligible patients who originated from spoke sites. Therefore, the true number of patients not randomised because of spoke sites is likely to be higher.

A total of four patients were lost because the surgeon decided against recruiting the patient. These patients were all from AUH and most likely excluded due to the surgeon(s) lacking equipoise. This is surmised because all surgeons at AUH were supportive and contributed patients. Approximately half of these surgeons use FS in their normal practice. Therefore, if a surgeon declined to recruit an eligible patient, it is most likely due to strong convictions about the benefit of FS (both in favour and against).

A total of three patients were lost because investigators felt that the patient's social circumstances were such that they would hinder compliance with the trial. Whilst this may have been for genuine reasons and in the patient's best interest, social issues were not an exclusion criterion. Every eligible patient should have had the opportunity to decide upon their participation. Investigators not recruiting patients who met eligibility criteria for social reasons were inadvertently allowing selection bias to enter the study. This behaviour would need to be addressed prior to a definitive trial through education.

8.1.2.3 Patients lost to follow-up

Overall, loss to follow-up was not a significant issue and, where it did occur, was due to conflicts between clinical and trial related follow-up. A total of seven (13%) patients who were recruited did not make it to the second follow-up visit. However only three of these were successfully randomised and revealed. The others were withdrawn before surgery as they no longer met eligibility criteria. In all three cases the patient was not willing to attend their second follow-up visit because the 4 – 6 week window did not coincide with their clinic visit. PROMs like the WHQ can be used by patients to report trial outcomes without the need for specific follow-up visits. For example, they can be employed via smart phone apps or telephone interviews. Consideration should be given to the development and validation of PROMs specific to HNS that address the priorities of patients and are suitable for remote completion by patients.

8.1.3 Outcomes related to trial conduct

8.1.3.1 Protocol adherence

A series of electronic checks within the eCRF were in place to monitor compliance with the timing of the allocation reveal. Once the patient was randomised, the surgeon was sent an email containing a password protected link to reveal the allocation. The time and date of this reveal was cross referenced with the start and finish times of surgery. The principle being that the surgeon should only reveal the allocation towards the end of surgery when the FS is used. This was thought to minimise the risk of performance bias because the surgeon did not know the allocation whilst performing the ND. Overall, there was good compliance with this aspect of the protocol. The median (IQR) length of surgery across both treatment arms was 2.2 hrs (1.8 – 2.6 hrs) and the median time to allocation reveal was 2.1 hrs (1.6 – 2.5 hrs). The histogram in Figure 24 shows that the protocol was breached for 1 patient where the surgeon revealed the allocation 6 – 8 hrs before the start of surgery. The event was investigated by undertaking a CAPA (see E.1 CAPA number 1). It was related to a misunderstanding of the

protocol early in the trial and was not repeated. In summary, allocation concealment until the point of wound closure was well adhered to and the electronic checks to monitor this were effective.

On one occasion the surgeon forgot their password to reveal the allocation (see E.2 CAPA number 2). The PI was contacted and unable to resolve the situation. Only the LCTU IT department had access to the treatment codes and could reveal the allocation over the telephone. Unfortunately, they were uncontactable even though attempts were made during normal office hours. This was particularly problematic because the allocation reveal was time sensitive, the length of General Anaesthesia was prolonged and the theatre list delayed. At the time a decision was made to empirically place the patient in the 'No FS' arm. This event highlighted a significant issue that needs to be resolved before a larger multi-centre trial is commenced. In a larger study there will be more surgeons over more sites and the time of allocation reveal may not occur within office hours. Therefore, a strategy to overcome this issue locally without time delay needs to be devised. A potential solution is a 'forgot password' tab on the login page. This gives the surgeon the opportunity to resolve the situation at once and without seeking help. Installing a trial 'hotline' in the IT department that is manned during office hours adds another layer of security. Staff are unlikely to ignore phone calls if they know it is from a hotline that will only be used in an emergency. If these measures fail, then the PI must take the default position of allocating the patient to the 'No FS' arm. Every time these events occur, investigators should contact the trials unit so a root cause analysis can be instigated (CAPA). The intention-to-treat principle would apply to the final analysis these cases.

8.1.3.2 Accuracy of data recording

Accuracy of data recording was broadly similar across both treatment arms and sites. As shown in Table 15 & Table 16, blood test results were the most frequent missing data items, especially clotting (PT, aPTT). The most likely reason for this being that these blood tests were not routine, and investigators were not willing to take extra blood samples for trial purposes. Blood results are not part of any analysis apart from the distribution of baseline characteristics. Given that

this REPT has shown that the randomisation strategy is effective, there is no requirement to collect these blood results in a future definitive trial.

Data on the length of surgery was missing in five patients. This outcome requires theatre staff to enter the start and finish time of surgery into a paper CRF. The RNs later transcribe this information into the eCRF. It is likely that paper CRFs were not fully completed because theatre staff are busy and may have forgotten. This missing data was overlooked by the trial co-ordinator who had responsibility for central data monitoring. Had the missing data been identified, RNs could have been instructed to check theatre records to complete data entry. The DEFeND REPT data monitoring plan (see A.8 Monitoring Plan) relied on central monitoring with triggered visits. A future definitive trial will have considerably more data and would benefit from additional scheduled monitoring visits. Furthermore, using email alerts sent to the Trial Co-ordinator (TC) and PI regarding incomplete data may improve the accuracy of data recording.

8.1.4 Fidelity of blinding process

Overall, there was a tendency for patients and RNs to think that the patient received the intervention whether they truly did or not. This phenomenon is reflected in the BI for patients and RNs. The BI and associated 95% CI for the FS arm was above 0 indicating patients and RN were able to correctly guess the allocation more than random guessing. However, in the 'No FS' arm the BI and associated 95% CI was below 0 (i.e. negative) indicating a tendency for 'opposite guessing' (i.e. incorrectly guessing the allocation more than random guessing). The observed pattern may be understood as 'wishful thinking' or 'lack of idea about control treatment', both of which are frequently seen in blinded trials. In general, blinding is a qualitative and empirically unverifiable issue. The BI is a function of the proportions of correct and incorrect guesses and therefore serves as proxy measure. 'Wishful thinking' could reflect a situation where anything looking like treatment is perceived as the interventional arm (e.g. patients in both arms underwent ND). Alternatively, it may represent an underlying tendency for patients to wish to receive 'better' treatment. The latter implies that patients believed being in the

interventional arm was better than being in the control arm. This may be a manifestation of how surgeons explained the trial to patients or how patients interpreted the PIS. If surgeons were convinced of the benefit of FS, they may have conveyed this bias to patients. If the patient had a smooth post-operative course, then they may have naturally believed they received the FS. The PIS (see A.2) was critiqued by patients from the Aintree Head & Neck Research Forum prior use in the study and no comments were made regarding bias. However, the wording would need to be reviewed prior to a definitive trial.

The behaviour witnessed in the choices made by RNs is more difficult to explain. Being familiar with the research process, they will know that the allocation was split equally between treatment arms. Despite this knowledge the RNs thought that patients received the intervention in most cases. There was also a tendency to select the response prefixed with 'somewhat believe' indicating a non-committal response. It is likely that the RN would have documented the patient's response before their own. Possible explanations for this behaviour may be a lack of equipoise or having an 'agreeable' personality trait. As with patients, bias towards the interventional arm may have been conveyed through surgeons and/or the PIS. Also, RNs would have followed the patient through their surgical journey and may have developed rapport. The RNs may have chosen to agree with the patient because they did not wish to undermine the patient's belief.

Surgeons demonstrated a distinctly different behaviour pattern to patients and RNs. They responded with the answer "don't know" rather than guessing in most cases. This is likely because they were familiar with the research process and were effectively blinded. The surgeon's behaviour and the wishful thinking phenomenon are associated with effective blinding.

8.1.5 Determining the minimal clinically important difference

The main aim of this analysis was to ascertain whether 'complications' was a suitable patient centred primary outcome for DEFeND. Unfortunately, the findings did not identify 'complications' as a dominant theme within responses. Avoidance of complications was important to

several patients and, as described in section 7.2.4, was linked to both wound healing and health economic benefits. However, more patients conveyed a wish to have improved wound healing that went beyond avoiding complications and included a return to normal function as quickly as possible. Based on these findings, it was possible to conclude that 'complications' represented a patient centred and pragmatic outcome. However, it was not clear if 'complications' represented the best primary outcome for DEFeND. The two dominant themes developed in this analysis generate more questions regarding the best primary outcome than answers. This demonstrates a need for a more robust qualitative methodology to be applied in a separate study.

In retrospect, expecting investigators to effectively explain the concept and relevance of MCID to patients was unrealistic. This is especially the case when investigators were untrained in qualitative interviewing and not given adequate time in busy clinics. Some patients did manage to convey relevant endpoints such as "a reduction in length of stay by one day", "half the length of stay", "wound healing 2-3 days quicker", "reduction in healing time by 50%". However, these responses were elicited from a small minority of patients and it was not possible to make any meaningful conclusions from them. Furthermore, because of the short comings of the methodology used in this analysis no inferences on MCID were made beyond the current sample of patients.

In summary, the analysis was hindered by a poorly conceived methodology that did not provide enough detail regarding the context of many responses. Two dominant themes were identified ("improved wound healing and recovery from surgery" and "less use of hospital resources") but further (separate) qualitative work is required to delve further into patient experiences and understand their priorities more fully. Whilst 'complications' and 'length of stay' were found to represent patient centred outcomes, it appeared that patients additionally prioritised the speed and quality of healing. Therefore, outcome measures like the Clavien-Dindo classification and 'time to discharge' may not have gone far enough to elicit the full extent of patient priorities.

8.1.6 Relevance of learning curve

It was not possible to use the findings of this REPT to quantify or even identify the presence of a learning effect associated with using FS in ND. This is because the sample size was too small and individual surgeons did not perform the intervention frequently enough to track their performance or provide surgeon specific metrics. The data raised the possibility that the efficacy of FS may have been dependent on either surgeon experience, dissection of level I or a combination of these factors. However, it was not clear which of these two factors was the most important. The findings of this REPT highlight a need to undertake further research to establish whether a learning effect exists prior to a definitive trial. This future research should include an estimation of the time required by each surgeon to overcome the learning effect. The data may be used to guide the decision on how to control for learning curve in the definitive trial i.e. implementing entry criteria for surgeons (credentialling) or adjusting for learning effect in the final analysis.

It was previously argued that extrapolating the learning curve data taken from a small number of surgeons and applying it to the wider surgical community was adopting a “one-size-fits-all” approach to surgical learning. Due to individual differences in learning, if this data is used to set the parameters for credentialling surgeons it is possible that surgeons who meet the entry criteria will be at different stages in their learning curve. Ideally, surgeons should be permitted to participate in the trial once they have reached the asymptotic part of their learning curve regardless of the parameters set by analysing the data from a small number of surgeons. The alternative to this approach would be to use the Bayesian hierarchical model described by Cook(177) and adjust for learning effect in the final analysis. At first glance this approach appears to be the most pragmatic because it does not require credentialling. However, for it to be effective, Cook recommended that the definitive trial include at least ten different surgeons who perform the intervention at least ten times.(177) In essence this approach may also result in using the data from a small number of surgeons and extrapolating their learning curve on to others. Additionally, within a busy NHS surgical practice, the operating surgeon is not always

the named consultant. Ensuring ten surgeons perform the intervention at least ten times may be prohibitively difficult within the context of a multi-centre surgical trial. Indeed, it may be argued that taking measures to ensure that only certain surgeons operate on trial participants is a very explanatory design feature. Therefore, within the context of a pragmatic surgical trial there is no single ideal method of controlling for learning curve. This argument justifies the need for separate research into quantifying the possible learning effect of using FS in ND.

The data presented on surgical learning curve has major implications on quality assurance in a future definitive trial. Credentialling of surgeons was not thought to be necessary prior to recruitment into the DEFeND REPT and the intervention was delivered entirely flexibly and without monitoring. When designing the trial, it was thought that this approach would move the trial more towards the pragmatic end of the continuum. The justification for not credentialling surgeons was based on the assertion that using FS in ND did not require the acquisition of new skills. If a surgeon was skilled enough to perform a ND it was presumed they would have the necessary skills to correctly administer FS. Although this study did not confirm the presence of a learning effect, there was enough difference in performance between the experienced and inexperienced surgeons to question this previously held presumption. Even though surgeons were not required to acquire new skills, they were required to familiarise themselves with the protocol and this would inevitably require a period of learning. Like most surgical techniques, the administration of FS in ND is technique sensitive and requires adherence to the manufacturer's procedural steps. Because some surgeons were learning on trial participants, the clinical outcomes reported in this study are likely to be subject to type II error. This needs to be taken into consideration when using the clinical data to guide the appropriateness of a future definitive trial.

It was argued that the role of standardisation and monitoring of the intervention was related to whether the per protocol analysis of a definitive trial would influence the uptake of FS in ND amongst the surgical audience if the ITT analysis is negative. As already discussed, the pragmatic approach is to deliver the intervention flexibly and conduct an ITT analysis that

demonstrates ‘effectiveness’. Within a pragmatic trial design, the outcomes of the ITT analysis are the most important because the prognostic balance between arms afforded by randomisation is preserved. The per protocol analysis is an inherently biased interpretation of the results. Therefore, if the per-protocol analysis is going to be disregarded, what is the justification for the additional resources and cost associated with monitoring the fidelity of the intervention? Based on the results of the REPT, the counter argument to this is that if a trial is delivered with poor compliance to the fidelity of the intervention the results will be subject to type II error. In the interest of transparency, this information should be reported in the final publication. Therefore, within the context of a pragmatic HNS trial the intervention should still be delivered flexibly but also monitored so that compliance can be accurately reported. As previously discussed in section XXX, the best way to monitor compliance in a future DEFeND trial would involve mobile video cameras filming both the preparation and administration of FS. This footage would be monitored centrally by sites sending either a secure online file or Secure Digital (SD) card to the CTU. In addition to monitoring the intervention the date and time on the screen would be cross-referenced with the patient’s unique identification number, allocation, start and finish times of the surgery.

8.1.7 Clinical outcomes

8.1.7.1 Clavien Dindo classification of surgical complications

As already discussed in section 6.2.1.1, the Clavien-Dindo classification (Table 1) is a generic and widely used tool that meets the definition of a pragmatic outcome measure. The CCI is a more recent tool that is derived from the Clavien-Dindo classification and accounts for the increased burden of multiple complications. Furthermore, the CCI converts the Clavien-Dindo classification, which is an ordinal outcome measure, into a continuous outcome measure. This quality makes it more useful in clinical trials because there is evidence that it is more sensitive at detecting differences in treatment effect and can reduce the required sample size.(210) The

authors of the CCI recommend using a MCID of 10 points as this corresponds to one grade of difference in the traditional Clavien-Dindo classification.(210)

Because the Clavien-Dindo classification is a generic tool, grading is open to interpretation when applying it to specific HNS complications. For example, Monteiro et al found that there was imperfect inter-observer reliability in scenarios where patients underwent a surgical procedure that did not require returning to the operating theatre.(137) To avoid this issue within the context of DEFeND, the severity of common/established complications associated with ND were graded and provided to investigators as a guide to conform to the Clavien-Dindo classification (see Appendix D. Clavien-Dindo Classification of Surgical Complications Adapted to Common Head & Neck Complications). The table in Appendix D. was included in the Protocol (See A.1) for investigators to use as a reference if they had doubts regarding appropriate grading of a complication. Furthermore, the complication form in the eCRF (see B.9) was designed to mirror the table in Appendix D. by asking investigators to grade the complication based on a description rather than allowing them to freely insert a grade. It was thought that providing a description would help reduce inter-observer variability. Examples of where the Clavien-Dindo classification may be suboptimal for HNS include patients who develop a deep space neck infection after ND and undergo drainage and packing of the wound on the ward. This complication may either be classified as grade I or grade IIIA. The neck wound often needs to be packed repeatedly, this will be uncomfortable for the patient and prolong hospital admission. On this basis, the most appropriate grade is IIIA but some investigators may report it as grade 1. Another example of where the Clavien-Dindo classification may not represent the significance of the complication adequately is in the management of oro-cutaneous communications or fistulas between the upper aerodigestive tract and the ND skin incision. In patient who undergo resection of a primary mucosal tumour and neck dissection, it is common for saliva and food debris to collect around the resection wound and leak into the neck. Under these circumstances a patient may be kept ‘nil by mouth’ and fed via a nasogastric tube until the leaking wound heals. This complication would be classified as a grade II. However, the patient’s experience of not being allowed to eat and a prolonged hospital admission does not seem

proportional to a grade II. This is in stark contrast to a patient who requires a course of oral antibiotics for a superficial wound infection that would also be grade II according to the Clavien-Dindo classification.

In terms of interobserver variability, the steps taken to minimise this issue were considered effective. Having a description of the grade for each of the most frequently anticipated complications within the eCRF worked well. Neither sites reported difficulties with interpretation or implementation. On reviewing the reported complications, all events were correctly graded by sites except for one. This exception was related to a site considering premature removal of a drain as a complication.

The results from the DEFeND REPT suggest that FS did reduce the CCI. Whilst the effect size was small, the results of this study may have been subject to type II error due to a lack of credentialing and possible learning effect. This study was not powered to detect a difference however, the results were used to decide upon the need for a definitive trial. Given the concerns regarding type II error, the overall CCI results were considered in combination with the CCI results for 'experienced' surgeons shown in Table 22. These surgeons would have likely met any credentialling criteria and had stabilised in their learning curve. The results in Table 22 suggest that the effect size was slightly larger when FS was used by 'experienced' surgeons, however, it was still less than the suggested MCID of 10 points.

The data from the semi-structured interviews used to determine the MCID suggested that. whilst 'complications' represented a patient centred outcome, it appeared that patients additionally prioritised the speed and quality of healing. Therefore, outcome measures like the Clavien-Dindo classification may not have gone far enough to elicit the full extent of patient priorities. Using a generic tool like the CCI may compromise the definitive trial by not not accurately representing the health experiences of patients. Since the choice of outcome measure is critical to trial design, a suboptimal instrument will result in suboptimal answers to the research question. These findings support the need for further qualitative work to delve further into patient experiences and understand their priorities more fully.

8.1.7.2 Drain outcomes

This study demonstrated that the collection of drain volume and removal outcomes were labour intensive for QVH due to the requirement for real time data entry and the pressures this placed on research support. Furthermore, they did meet the definition of pragmatic outcomes. None of the recruited patients prioritised drain volume or drain removal as an important outcome when asked about their priorities in the semi-structured interviews used to determine MCID. LoS appeared to be a far more relevant, and therefore pragmatic outcome measure. However, LoS is an incredibly short-term outcome measure that does not capture the full impact the surgery has on a patient and is affected by non-surgical and social factors. For this reason, drain outcomes should be eliminated from the definitive trial and LoS should be an important secondary outcome. These changes will mean sites will no longer be required to enter data in real time or change the type or number drains they normally use. With drain outcomes being eliminated from a definitive trial design the eligibility criteria can extend to include bilateral NDs. Excluding drain outcomes will thereby make the trial design more pragmatic as previously discussed in section 5.5.2.2.

8.1.8 Patient reported outcomes

8.1.8.1 Neck Dissection Impairment Index

The NDII is validated for use in patients undergoing the types of NDs that were performed in this study, however it is not validated for use so soon after surgery. NDII has been validated for use at a minimum of 11 months postoperatively, however in this study it was used after just 4 – 6 weeks. This is because postoperative RT is known to influence the outcome of NDII.(147) It was thought that performing the NDII before the patient started postoperative RT would enable a less confounded evaluation of FS in ND. The results of the REPT suggest that the use of NDII in DEFeND was both acceptable to patients and feasible. Signal form the informal assessment suggests that FS may improve the NDII at 4 – 6 weeks. In keeping with a pragmatic

approach, NDII should be assessed after 11 months irrespective of the effects of postoperative RT.

8.1.8.2 Neck pain scale

The results of the neck pain scale suggest that collecting this data is both acceptable to patients and feasible. However, pain scores were low for both arms and there was no signal suggesting FS influences post-operative pain. For this reason, the inclusion of pain as an isolated outcome measure in the definitive trial is superfluous. The results do not preclude the use of pain outcomes within a broader PROM specific to HNS.

8.1.8.3 Wound Healing Questionnaire

The WHQ has been validated for patients undergoing abdominal surgery and is designed to be used within the same time frame as it was used in this study. Results suggest that the WHQ was both acceptable and feasible for use in DEFeND. Informal analysis suggests that FS may reduce the WHQ score albeit not to a statistically significant level. Furthermore, the WHQ has potential to be a very good discriminator between HNS patients who have SSI and those who do not. Data from this study was comparable to the data published for the Bluebelle study in terms of sensitivity and specificity of diagnosing SSI.(149)

In summary, the data suggest that instruments like the WHQ can be successfully deployed in HNS trials and, in keeping with the findings of the review in section 6.1, development of PROMs specific to HNS is an important priority.

8.2 Strengths & Limitations of this Work

8.2.1 Site selection

This study was set within two UK hospitals offering tertiary HNS services (AUH and QVH). The decision to select two centres was considered important because a future definitive trial with a pragmatic design would need to be multi-centre. Both institutions met the minimum requirement for participation outlined in section 5.4. As the lead site AUH had a strong research portfolio in HNC research. Four of the academic surgeons had experience as Chief Investigators (CI) and a dedicated team of HNC Research Nurses (RN) were on hand to optimise recruitment and trial conduct. This research background and infrastructure certainly contributed to the strong recruitment performance demonstrated by AUH in this study.

QVH was selected because it was thought that it was representative of most non-academic centres across the UK. It had fewer RNs and considerably less experience in delivering RCTs. Understanding the experiences of QVH in delivering DEFeND REPT was thought to be key to the design of the future definitive trial. As previously mentioned in section 4.4, the decision to select QVH as a second site over other possible sites was based on the PhD candidate and CI having close links. As expected, QVH did not recruit as well as AUH. However, the degree to which they struggled was not anticipated. They failed to meet their target of recruiting two patients per month. Several reasons were identified as to why recruitment problems were encountered. Firstly, It was not recognised that spoke sites could be opened as PICs which meant that the full potential of recruitment at QVH may not have been realised. Secondly, two of the seven surgeons at QVH did not recruit because they were not willing to make changes to their practice for trial patients. This issue should have been identified earlier and, if possible, consensus amongst surgeons reached. If more surgeons did not accept the protocol, a different site should have been considered. Ultimately, finding consensus amongst a body of surgeons can be very difficult and one has to accept that this may not be possible despite best efforts. The main issue was the requirement for a single drain when they would normally use two. This

issue will be eliminated in a definitive pragmatic trial because drain outcomes will not be measured and surgeons will be allowed to continue with their usual practice. Removing drain outcomes will also address another issue that QVH faced in terms of real time data entry. QVH found recording trail outcomes in real time labour intensive because they did not have enough availability of investigators trained in recording data in the eCRF.

Using QVH as the second site was valuable because it identified problems with the trial design not encountered by AUH. Within the context of a future multi-centre trial, selecting sites with good research infrastructure will undoubtedly benefit recruitment. However, within the field of HNS research, these sites a few and far between. In order to conduct multi-centre trials in HNS selecting sites that have relatively little experience is likely to be a necessity. Whilst the recruitment figures from QVH may suggest that site selection was a weakness of this study, in fact from a PFS perspective, their selection was a strength. As a result of the experiences reported by QVH, the need for further pre-trial work and the need for significant changes to the trial design have been identified (see section 9.1).

8.2.2 Pragmatic trial design

The aim of the DEFeND REPT was to evaluate the feasibility of a pragmatic trial design and assess whether these design features worked well together. Through delivering the study and developing a greater understanding of pragmatic and explanatory trial designs, several misconceptions in the trial design have been identified. Pragmatic clinical trials should focus on outcomes that are relevant to patients, healthcare professionals and decision makers. The most pragmatic outcomes are those that are of obvious importance to patients and measured in the same way they would be in usual care.(109) In this study investigators were asked to use a single drain, to use a specific drain that had a collection bag that could be emptied into a measuring cylinder, to enter drain volume data into the eCRF twice daily and in real-time, to allow a computer algorithm to decide when the drain should be removed. All these aspects of the protocol are very much on the explanatory end of the continuum. In a pragmatic trial,

investigators should be allowed to use however many drains of whichever type they usually do. Furthermore, assessments of drain volume and removal should also be in keeping with their normal practice.

Using the PRECIS-2 tool(109), an assessment can be made of how pragmatic the original DEFeND REPT design was and compare it to an ideal definitive trial design (based on what has been learnt by undertaking this work).

1. **Eligibility criteria.** In keeping with a pragmatic approach, inclusion criteria were broad and exclusion criteria were kept to a minimum. However, the exclusion of patients who required less than three levels dissected or required a bilateral ND would prevent the eligibility criteria from scoring maximum points in terms of pragmatism. As already discussed, a future definitive trial would stratify for the extent of surgery and include these patients. Participants were broadly representative of the patients that would receive the intervention in usual care, and they were not excluded on the basis of tests that are not applied in usual care.
2. **Recruitment.** In keeping with a pragmatic approach, participants were recruited from a normal clinical environment with no overt recruitment effort. 52.5% of eligible patients were recruited and it is not clear whether this resulted in certain groups of patients being excluded. Therefore, it is not possible to be certain whether the recruited patients were truly representative of the patients in whom the intervention will be used in usual care. Unfortunately, this is a problem with all surgical trials as recruitment is never even close to 100%.(105, 113) Recruitment may have been improved by opening spoke sites as PICs to truly represent the normal clinical environment. The trial design pertaining to recruitment was therefore not as pragmatic as it could have been.
3. **Setting.** The selection of both an academic and non-academic site was a pragmatic design feature. Furthermore, these sites were located in very different parts of the country in terms of the demographic of the population (for example, a deprived urban population in the Northwest versus a relatively affluent semi-urban/rural population in the Southeast). Whilst only two sites were selected for the REPT, several more sites

would be selected for the definitive trial thereby mirroring the setting in which the results of the trial will be applied.

4. **Organisation.** According to the authors of the PRECIS-2 tool, a pragmatic approach should mirror how care is organised and delivered in usual care and not make use of extra resources. Increasing staffing levels to deliver the intervention, providing significant additional training, requiring investigators to have a minimum level of experience or certification all make the design more explanatory.(109) In the DEFeND REPT there was no requirement for extra staff, the only training provided was at the site initiation visit and through educational videos and surgeon credentialling was not required. On this basis the trial design was very pragmatic. However as previously discussed, surgical interventions are often associated with a learning effect. Evaluating the intervention without accommodating for the learning effect (e.g. through credentialling) will have significant implications on both quality assurance and the interpretation of results in terms of type II error. Therefore, a definitive DEFeND trial cannot and should not attempt to meet these requirements for a pragmatic design. A surgical trial can only be truly pragmatic in terms of organisation if the intervention is already widely used and it is no longer associated with a learning effect. Therefore, a truly pragmatic surgical RCT should only need to be conducted under fairly exceptional circumstances (e.g. widely adopted and established surgical intervention is compared to other widely adopted and and established interventions for the treatment of the same condition).
5. **Flexibility of delivery.** According to the authors of the PRECIS-2 tool, a pragmatic approach would mirror how the intervention will be delivered in usual care and allow investigators the flexibility to deliver it as they see fit. Having a highly specified protocol-driven intervention and having measures in place to monitor compliance of those delivering the intervention would make the trial more explanatory.(109) In the DEFeND REPT surgeons were permitted to perform the ND as they normally would. Clear instructions on how to store, prepare and administer FS were provided via the site initiation visit, educational videos and laminated posters located within operating theatres.

However, surgeons could choose to ignore these instructions and deliver the intervention however they wished without the central trials team knowing there has been a protocol violation because of the lack of monitoring. These design features made the DEFeND REPT very pragmatic. As previously discussed, within the context of a surgical or complex intervention, a pragmatic approach should permit flexibility of delivery but should also monitor the fidelity of the intervention so that compliance can be reported in the final publication. Whilst the reporting of compliance will not change the outcome of the trial, it will facilitate transparent reporting of the results and enable readers to conclude for themselves whether the fidelity of the intervention was a factor in the trial outcome.

6. **Flexibility of adherence.** Because FS was administered once during surgery, the participant's flexibility of adherence to the intervention was not a significant issue. Three patients were incorrectly excluded from the REPT by investigators because they felt that the patient would not comply with the trial protocol due to social reasons. However, this was an independent decision by investigators rather than a specific fault in the trail design.
7. **Follow-up.** In keeping with a pragmatic approach, the DEFeND REPT tried to keep extra visits beyond those required in usual care to an absolute minimum. Two patients were lost to follow-up because the second follow-up visit did not coincide with their routine clinical appointments. The most pragmatic designs often avoid any follow-up altogether and collect data via other means e.g. electronic medical records. Collecting more extensive data than would be typical outside the trial and having longer follow-up appointments all make the design more explanatory.(109) Measuring outcomes like return to theatre, length of stay, hospital readmission and mortality can be done without the need for patients to be specifically followed-up for the trial. However, as demonstrated in the review of surgical COS, 'humanistic' outcomes play an important role in evaluating surgical interventions. Within the field of HNS very few 'humanistic' outcomes are recorded routinely outside of clinical trials, indeed there is a distinct lack of

such outcomes that are validated. An approach to recording 'humanistic' outcomes whilst keeping follow-up to minimum would be to employ smartphone apps that ask the patient to complete a validated PROM in their own time and without the need for a hospital visit. However, not all patients will have access to this technology or understand how to use it. It is therefore important to undertake pre-trial work to understand what proportion of patients will comply with this design feature. Care needs to be taken not to exclude patients on the basis of their ability to comply with technology. Therefore, having alternative approaches to be more inclusive are vital to keeping the trial design pragmatic.

8. **Primary outcome.** A pragmatic primary outcome is one that is significant to patients as well as being relevant to commissioners. Complications after surgery may be considered to be a pragmatic outcome because it is routinely evaluated in usual care as well as being relevant to patients and commissioners. Whilst the qualitative work presented in the MCID is fundamentally flawed, it does seem to suggest that patients prioritised the speed and quality of healing in addition to the avoidance of complications. Therefore, outcome measures like the Clavien-Dindo classification may not go far enough to elicit the full extent of patient priorities. Based on the findings of this study, further qualitative research is necessary. Firstly, to identify the priorities of patients and secondly to develop and validate PROMs that appropriately evaluate these priorities.
9. **Primary analysis.** In keeping with a pragmatic approach, a future definitive trial will employ an ITT analysis using all available data and not making special allowances. Adopting a per protocol analysis is an inherently biased assessment because the prognostic balance between arms afforded by randomisation is not preserved. However, within the context of a surgical trial, understanding the reasons for any differences between the ITT analysis and per protocol analysis may provide valuable insights into the intervention as well as providing readers with complete transparency of the results.

In summary, the PRECIS-2 wheels of the original DEFeND REPT design is compared in diagrammatic form to an ideal definitive trial design in Figure 30. The black line represents the original REPT design and the red line represents the future trial design. These wheels can be compared to the wheels of the published RCTs presented in Figure 11. It is clear to see that both original and future DEFeND trial designs are towards the pragmatic end of the continuum and both are markedly more pragmatic than the trials by Vidal-Perez et al(94) and Huang et al(95). The shapes of the original and future DEFeND trials are different and reflect some of the key learning points from undertaking this work as described above. It is important to note that even in an ideal trial design, the PRECIS-2 wheel does not score maximum pragmatism points in every category. Herein lies the difference between a pragmatic HNS trial design and a generic pragmatic drug trial. The former involves the delivery of a complex intervention with an associated learning effect. As previously discussed, it is important to quantify this learning effect and employ methods such as surgeon credentialling to ensure that the intervention is delivered by surgeons who are in the asymptotic part of their learning curve. Furthermore, whilst the intervention should be delivered flexibly, it is important to monitor the fidelity of the intervention to enable a robust and transparent analysis (that includes both ITT and per protocol analyses). With future qualitative work it will almost certainly be possible to improve the primary outcome measure to reflect the priorities of patients in a more comprehensive manner. If the primary outcome takes the form of a PROM that can be implemented through an App, the burden of hospital follow-up appointments may be significantly reduced. However, it is unlikely that this PROM will be collected in routine clinical practice, at least initially. Conducting truly pragmatic trials is hugely challenging in the current HNS research landscape. This is because engaging surgeons working in non-academic centres can be difficult and often leads to recruitment problems. Ultimately this issue is complex and multi-factorial. Fletcher et al reported that use of qualitative work to identify and overcome barriers, reduction of the clinical workload associated with participation in RCTs and the provision of extra training and protected research time were all potentially effective measures to improve engagement.(220) Additionally, pragmatic trial designs rely on large numbers of patients. HNC is not as prevalent in the

UK as other cancers such as breast, prostate, lung and bowel.(221) Therefore, a relatively higher proportion of HNC patients from fewer centres need to be recruited to meet the large sample sizes required for pragmatic trials.

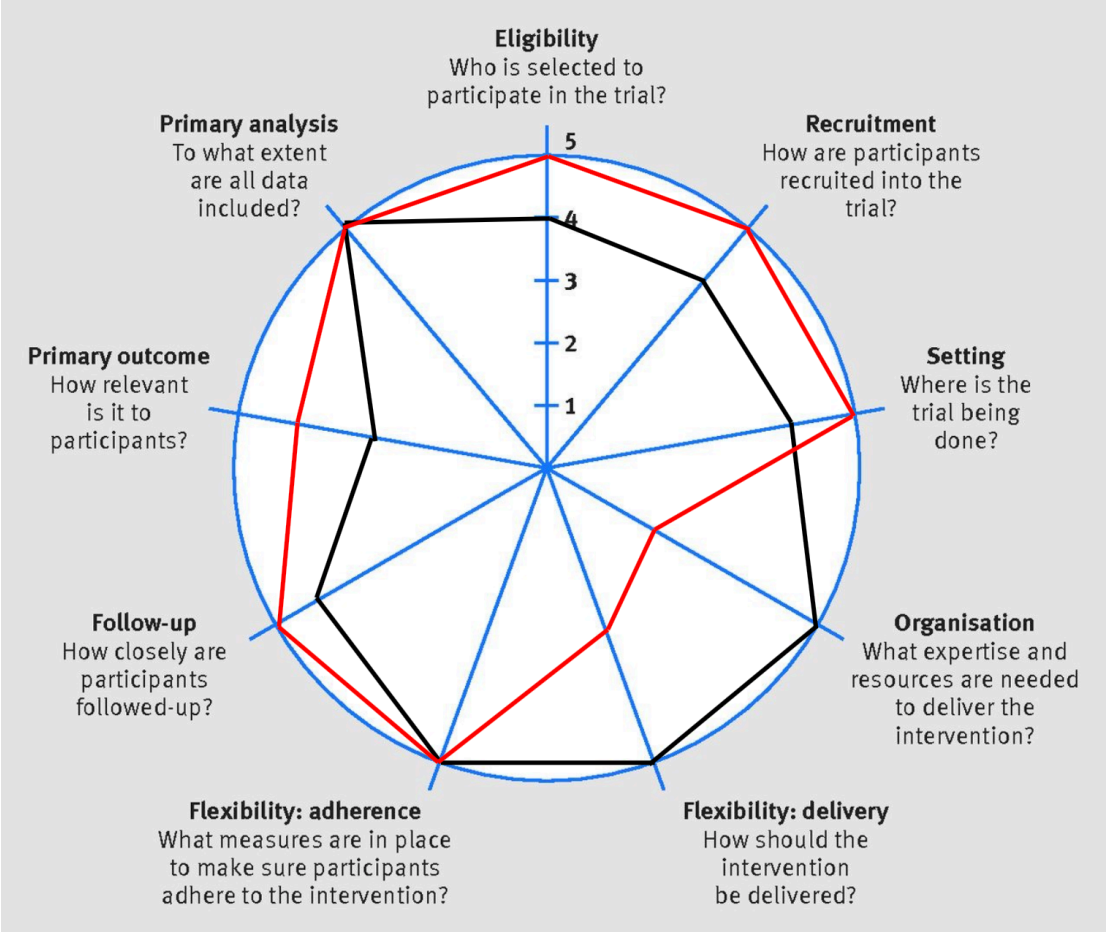


Figure 30 PRECIS-2 wheels for originial DEFeND REPT trial design (black line) and future definitive DEFeND trial design (red line).

8.2.3 Methods used to explore recruitment

Overall recruitment to the trial was successful as the recruitment target was reached ahead of schedule. This was driven by the success of AUH which compensated for the problems faced by QVH. The methods used to explore recruitment were suboptimal because the opportunity to use formal qualitative methods to delve deeper into the recruitment problems was not taken. The recruitment challenges faced by QVH were identified through unstructured interviews with

the PI. Only having the PI provide feedback is flawed because he may have chosen to exclude certain issues raised by other investigators. Whilst the PI may not have considered these issues to be important or relevant, it is important to have given all investigators an opportunity to voice their opinions. Afterall, their concerns may have been highly relevant to the design of a future trial. Having said this, there was no reason to suspect the PI withheld any important recruitment challenges as all the points raised were encountered by the PhD candidate in his regular communication with sites.

In hindsight, undertaking formal semi-structured interviews or surveys with investigators at site (including research nurses, surgeons, ward nurses and theatre staff) would have been beneficial and provided much more granular information on any recruitment challenges. By conducting these interviews early in the REPT it would have been possible to introduce recruitment interventions, such as the 'QuinteT Recruitment Intervention', to understand the problems in greater depth and enable effective strategies to address them.(222) It would be fair to conclude that the value of such qualitative methods in the DEFeND REPT was underestimated at the start of the study.

8.2.4 Electronic case report form design

The design of the eCRF modernised many aspects of trial conduct when compared to other trials led by the NWSTC/LCTU which were more paper based. The key design features were:

8.2.4.1 Informed consent process

Once sites had consented a patient, they ticked the relevant box in the Screening Form (B.1) which generated an automated email to the central trials team. This informed them that an informed consent form (ICF) was waiting to be authorised on the LCTU's secure server. The process required two members of the central trials team to independently authorise the ICF and electronically sign-off in the Randomisation Form (B.6). The last person to sign-off permanently deleted the electronic copy of the ICF.

The previous approach used by the LCTU required sites to fax a copy of the ICF for central authorisation. The faxed copy was then stored in a locked filing cabinet for a pre-specified period of time beyond completion of the trial. This approach required storage space as well as being subject to strict data protection rules to preserve patient confidentiality. The approach used in the DEFeND REPT streamlined the process and did away with the need to store copies of the ICF in the LCTU premises. This process was authorised by the LCTU senior management and the Quality Assurance team.

In an issue not directly related to the eCRF, the REC waived the need for a minimum of 24 hours between patients being informed of the study and signing the ICF. This was thought to be advantageous as it allowed patients to consent to the trail without the need for further hospital visits, especially if they lived far from the site. However, if spoke sites were opened as PICs, it can be argued that this deviation from the norm is unnecessary. This is because the consent process for the trial can be more easily harmonised with the consent process for surgery when patients are seen at spoke sites. There is no reason to suspect this change in process will have any impact on the use of the eCRF.

8.2.4.2 Randomisation and reveal process

Before randomisation could be performed the pre-randomisation checklist (Randomisation Form B.6) needed to be completed. This involved authorisation of the ICF (as described above), authorisation of eligibility criteria by the PI, completion of the baseline NDII and Neck pain Scale and a final sign-off by an investigator to confirm the checklist was complete. This process was designed to prevent patients being inappropriately randomised. However, it was not able to prevent three patients being randomised but not revealed. These patients had last minute changes to their treatment plan which meant they were no longer eligible and it was not possible for investigators to predict these scenarios. Patients with HNC often have multiple co-morbidities and occasionally may become too unwell to undergo major surgery. Furthermore, it is not uncommon for patients to have particularly fast growing or aggressive tumours that

become inoperable in the weeks that lead up to surgery. Overall, the pre-randomisation checklist worked smoothly and did not create any barriers to the effective running of the trial.

Once randomised, an automated email with a link to reveal the allocation was sent to the surgeon. The date and time of the allocation reveal was cross-referenced to the start and finish times of surgery. This was an entirely novel approach to revealing the allocation at a specific time point during surgery to minimise performance bias. It was therefore not surprising that all the CAPAs reported in the trial were related to this process (Appendix E.). The process of cross-referencing the time of allocation reveal to the start and finish times of surgery worked very well and highlighted a deviation in the protocol by a surgeon very effectively. However, the process was time dependent and the importance of having fail safes and effective support for surgeons from the NWSTC/LCTU was identified as result of this REPT. Overall, the electronic processes involved in the randomisation and reveal process were effective and could be improved with some relatively straightforward changes.

8.2.4.3 Reporting outcome measures

Prior to commencing the study it was known that the Clavien-Dindo classification was prone to inter-observer variability when used in HNS.(137) To counteract this issue, the eCRF was designed so that a description of the severity of common complications was provided to investigators (B.9). This approach proved to be effective for common complications. There was only one instance when the investigator reported the premature removal of a drain by a patient as a complication under the 'other complication' option. Although this deviated from the protocol, it was not a complication. The eCRF could be improved by adding a note to clarify this position.

As already discussed, the Drain Output Data form (B.10) was a very explanatory design feature and should not be included in a definitive trial. From a technical standpoint, the computer algorithm worked very well in guiding investigators when to remove the drain. The form was designed to minimise detection bias. However, QVH found it labour intensive because of the requirement for real-time data entry and some surgeons resisted the requirement for using a

single drain. Understanding why this form was counterproductive in delivering a pragmatic trial was a key learning point from this REPT.

In summary, the eCRF was successfully deployed and some key learning points in the design were learned through the REPT. Accuracy of data recording was to a high standard with very little missing data that was important to the trial outcomes. In a definitive trial, the same framework can be safely used once the changes discussed have been implemented.

8.2.5 Other trial processes

8.2.5.1 Randomisation strategy

The randomisation strategy was effective as evidenced by an even distribution of baseline and surgical characteristics across treatment arms. Any differences in baseline characteristics noted between study arms are likely to be evened out further in a study with a larger sample size. A larger sample size will also permit the use of further stratification criteria such as extent of surgery (as discussed in section 5.5.1.2 and 5.5.2.2). 20% of patients declined to enter the study implying most patients were supportive of the trial and accepting of randomisation.

8.2.5.2 Blinding strategy

The blinding strategy was effective as evidenced by the data from the Bang Blinding Index (BBI). Interestingly both patients and RNs exhibited the 'wishful thinking' phenomenon. This may have been due to recruiting surgeons lacking equipoise and patients and RNs picking up on cues relating to the benefits of FS in ND rather than any counter arguments e.g. the lack of high quality supporting evidence.

8.2.5.3 Qualitative methods used to determine the minimal clinically important difference

There are several limitations to the applied qualitative methodology used to determine the MCID. Firstly, the semi-structured interviews were conducted by untrained investigators in a

busy clinic environment. Secondly, the investigators summarised the patient's comments into the eCRF thereby processing the information and potentially applying personal biases (both in the selection and interpretation of what was written). Thirdly, only patients who had completed follow-up were interviewed. It is likely that these patients considered the potential benefits of FS mentioned in the PIS favourably. Patients who did not participate or did not complete follow-up have equally valuable views and opinions that were not collected. Ideally, a separate study conducted by trained investigators using audio recordings of interviews would have provided a much richer and more representative source of qualitative data. Therefore, the findings were not generalisable to patients outside of the current study.

8.2.5.4 Safety

The safety plan was not tested within the REPT as no SAE/SUSARs were reported throughout the study duration and no patients needed to unblinded. The Safety plan used in the REPT was derived from LCTU standard operating procedures and therefore there is no indication to change this process in a definitive trial. It is reassuring to note the that use of FS in ND can be considered safe for patients.

8.2.6 Lack of pre-trial work

Undertaking a survey of recruiting surgeons prior to commencing the trial to establish their usual practices may have demonstrated issues with potential protocol compliance. Such a survey could have also been used to help select the sites most likely to comply with the protocol. As already discussed, selecting sites based on their likelihood to comply with the protocol would have been an explanatory design feature. Ultimately much of the success of trials is judged on recruitment. A trial that has sufficient numbers of patients to answer the research question is more valuable than a trial that rigidly sticks to ideals and fails to recruit enough patients. Within the context of the REPT, QVH provided valuable information to guide future trial design and their inclusion was considered a strength. In a definitive trial however, the aim would be to recruit as many patients as efficiently as possible. As already discussed, opening sites like

QVH in a definitive trial may be a necessity because it is representative of many non-academic HNS centres. Using a survey as described above would enable the central trial team to prioritise the order of opening centres. This could be done by opening centres that are more likely to recruit well and comply with the protocol ahead of others.

8.3 Contribution to Existing Knowledge

8.3.1 Fibrin Sealants in neck dissection

As a REPT this study was not designed or powered to detect a difference between treatment arms. Therefore, it is not possible to use this data to add to the existing knowledge regarding the effectiveness of FS in ND. At the start of this study several justifications for conducting an REPT prior to a definitive trial were provided. These will be discussed individually below:

8.3.1.1 Recruitment

There was uncertainty regarding the timing of the DEFeND trial and whether individual surgeon equipoise will impact on their ability to convey equipoise to patients and their willingness to recruit patients. The recruitment data from this study paints two contrasting pictures. AUH performed very well and demonstrates that an academic HNS centre is capable of recruiting very well to surgical trials. Given the evidence of the 'wishful thinking' phenomenon demonstrated by the BBI, the AUH surgeons may not have conveyed equipoise effectively. However, if this was the case, it did not stop patients consenting to the study. This may be because FS is considered a safe intervention and has no bearing on the patient's cancer treatment. The trial may have been easy to recruit to because of the low risks involved. Therefore, the timing of the trial and individual surgeon equipoise did not seem to have an impact on recruitment in AUH.

The performance of QVH in the REPT was less than expected. Possible reasons for this have already been discussed in section 8.1.2.1. The findings from this study suggest that QVH did not struggle to recruit because of the timing of the trial. Instead, it was most likely due to

combination of trial design features that made participation laborious for investigators and a lack of surgeon engagement that may have been, in part, due to issues with equipoise. Changes to the trial design to make it less laborious, such as removing the need for real-time data entry, have been proposed and relatively simple modifications. Addressing surgeon engagement equipoise is more complex and ultimately requires a mixed-methods evaluation to understand the barriers. As reported by Fletcher et al this may include qualitative work to identify and overcome barriers, reduction of the clinical workload associated with participation in RCTs and the provision of extra training and protected research time. With the benefit of hindsight, it is recognised that opportunities to collect this data were missed by not incorporating robust qualitative methods (surveys, structured and semi-structured interviews) in the study design. Given the research landscape in HNS, PFS studies have an important role in minimising research waste and would benefit from the incorporation of mixed methodology to maximise the learning from the process.

8.3.1.2 Trial design

Randomising patients prior to surgery and revealing the allocation at a specific time-point intra-operatively was shown to be feasible. Previous trials led by the NWSTC/LCTU had problems with randomising patients intra-operatively for reasons discussed in section 3.2.3.3. However, randomising pre-operatively presented its own problems in this study. Three patients were randomised but later withdrawn from the study due to changes in treatment plan that meant they were not longer eligible. These patients would not have been lost if randomisation occurred intra-operatively at the point of wound closure. Given that these patients were a very small minority, the process of pre-operative randomisation and intra-operative reveal is still advocated. Increase the sample size of a definitive trial to accommodate for this eventuality would be required.

At the start of the study there was uncertainty whether the unblinded operating surgeons would have an influence of the fidelity of the blinding strategy. As already discussed, this was not born

out in the data from the BBI. Therefore, it is possible to effectively blind participants and investigators within a busy HNS practice.

8.3.1.3 Trial Outcomes

At the start of the study, complications were considered the most pragmatic outcome. Whilst the Clavien-Dindo classification represented the most widely used instrument to evaluate complications, there was uncertainty regarding how it should be deployed. This was because of concerns regarding inter-observer variability and the possibility of patients suffering multiple complications. Providing investigators with a description of the most frequently encountered complications rather than allowing them to interpret the classification themselves, eliminated any problems with inter-observer variability in this study. Furthermore, using the CCI rather than the traditional Clavien-Dindo classification eliminated issues with reporting patients who suffer multiple complications.

Whilst the qualitative work performed to determine the MCID was poorly conceived and delivered, it did raise the possibility that complications on their own might not go far enough to address the priorities of patients. The information gathered from trial participants can interpreted to suggest that patients not only want to avoid complications, but they also want their wounds to heal as efficiently as possible and minimise the use of healthcare resources. Using the CCI as the primary outcome measure may be an acceptable approach but there is currently no evidence that suggests it is the best option. Evidence from the review of COS presented in section 6.1 and the performance of the WHQ in trial participants suggest that PROMs developed specifically for HNS may be a more holistic and valuable way of evaluating interventions. Furthermore, PROMs can be completed by participants remotely, doing away with rigid follow-up visits. In summary, the dearth of HNS specific outcome measures has been recognised and that a reliance on generic instruments may be sub-optimal. Addressing this unmet need should be a research priority in HNS.

8.3.1.4 Trial conduct

The main question regarding trial conduct was whether the components of the trial worked well together. The findings of the REPT suggest that this was dependent on the research site. In AUH there were some teething problems that have been discussed in section 8.1.3.1 and were dealt with through a process of root cause analysis (CAPA). However, after these issues were addressed, the trial was delivered without problems. Whilst no protocol deviations were identified at QVH, they did report challenges with recruitment and labour intensiveness which have already been discussed in section 8.1.2. Perhaps the most important learning point from centres which rely heavily on a hub and spoke model for delivering HNS is the effective use of PICs. The findings of this REPT will help to harmonise the research process better with routine clinical care which should improve the performance of sites like QVH.

8.3.1.5 Fidelity of the intervention

This topic has already been discussed at length in both section 8.1.6 and 8.2.2. The findings of this REPT advocate the importance of identifying and quantifying learning effect and using this data to implement surgeon credentialling. The intervention should be delivered flexibly within the context of a pragmatic HNS trial but should also be monitored. It is accepted that reporting fidelity of the intervention through monitoring will not change the outcome of the ITT analysis. However, transparent reporting enables the surgical audience to make their own decisions regarding the influence of fidelity of the intervention on trial outcome.

8.3.1.6 Sample size

One of the aims of this REPT was use the clinical outcome data to estimate the sample size of a future definitive trial. However, numerous issues have been identified that would make such a calculation inappropriate. Currently there are questions over the best outcome measure and whether the CCI meets the expectations and priorities of patients. Furthermore, not adjusting for learning effect has potentially exposed the data to type II error. It is now recognised that

considerable further research is required before the definitive DEFeND trial should be started (see Chapter 9. Future Work)

8.3.2 Head and neck surgical trials

Once described as a “comic opera”, surgical trials in the UK have advanced considerably in recent years both in methodological rigor and recruitment.(223) As this work has demonstrated, surgical trials are associated with numerous methodological challenges due to the complexity of the intervention and lack of surgeon equipoise. In keeping with the IDEAL framework, the development of surgical innovation involves the progression from explanatory studies evaluating efficacy to pragmatic studies evaluating effectiveness.(126) The DEFeND REPT provides an example of why conducting HNS trials with a truly pragmatic design can be problematic apart from in exceptional cases. As discussed, the implications of learning effect on surgeon credentialing and monitoring of the intervention are both areas that require careful consideration when designing a pragmatic HNS trial.

Overall recruitment to this trial was very good however, it was driven primarily by the academic centre. The performance of QVH is cause for concern for recruitment to pragmatic HNS trials as it is representative of many HNS centres across the UK. It is likely that many of the recruitment challenges reported by Kaur et al in 2013(105) still stand several years later. Many of the recruitment problems faced by QVH stem from a lack of research infrastructure leading to a lack of harmony between research processes with routine clinical care. Surgeons are the gate keepers to accessing patients with HNC and therefore their engagement with research is the key to unlocking improvements. This is largely a political issue for which much has been done in recent years not least by initiatives from the NIHR, Royal College of Surgeons and introduction of trainee research collaboratives. When designing pragmatic HNS trials, researchers need to take steps that help integrate the research process with routine clinical care. Key learning points from this work include making data collection less labour intensive and either integrating follow-up visits with routine clinical care or doing away with them all together. Whilst these are

all important points, the elephant in the room is the distinct lack of methodological research that identifies the research priorities of HNS patients and seeks to develop the best methods and instruments to evaluate them. Without this vital research, the quality of HNS research will fall behind other surgical specialties.

Chapter 9. FUTURE WORK

9.1 Changes to Trial Design

Throughout the discussion chapter several changes to the current trial design have been proposed. These have the potential to improve the performance of a definitive trial in both academic and non-academic HNS centres. The changes are summarised below:

1. In terms of recruitment lessons regarding the use of PICs have been learned. Sites that use the 'hub and spoke' model will have spoke sites opened as PICs. This will enable patients to be identified and given information about the trial earlier in their treatment pathway and harmonise the research process with normal clinical care.

2. Eligibility criteria will be extended to include patients who have two or more neck levels dissected and patients undergoing bilateral NDs. These changes are afforded by the abolishing the computer algorithm to decide on drain removal and stratifying patients based on extent of surgery.

3. Monitoring of Intervention is deemed important for a pragmatic HNS trial to facilitate transparent reporting of trial outcomes based on compliance with protocol. The proposed method for doing this involves the use of mobile video cameras placed on the surgeon's body and stored in an SD card for central evaluation.

4. Drain outcomes will be removed because they are no longer considered pragmatic. This will make the trial easier for non-academic sites because there will no longer be a requirement for daily real-time data entry. It will also facilitate the expansion of eligibility criteria (as mentioned above) and permit surgeons to use as many drains as they wish. The latter point being an issue for two QVH surgeons in the REPT. LoS was found to be particularly important to patients and will be included in a definitive trial.

However, using LoS as a primary outcome measure is problematic because it is incredibly short term and is influenced by external factors e.g. social issues that delay discharge. Whilst it is an important outcome, LoS is unlikely to provide a comprehensive evaluation of FS in ND. The CCI is a valuable and pragmatic outcome measure which has been shown to be feasible in a HNS trial however, it may not be an ideal choice. When questioning patients regarding the MCID, two dominant themes developed. These findings support the need for a more robust qualitative methodology to be applied in a separate study.

5. Whilst it was argued that the inclusion of a site like QVH was valuable to the REPT, having sites that are slow to open and recruit will be problematic in a definitive trial. In keeping with a pragmatic approach, these sites are important to be included, but not at the expense of the success of the trial. Therefore, as Fletcher et al.(220) reported, the use of pre-trial qualitative work is essential to identify and overcome barriers, reduce clinical workload associated with the trial, identify the need for extra training and protecting research time. Unfortunately, the value of this work was not fully appreciated prior to the REPT. Therefore, a further separate study is required prior to commencing the definitve trial to address outstanding issues particularly regarding surgeon engagement and equipoise. Data from this study can be used to better predict which sites are likely to perform well in a definitive trial so that they may be prioritised for opening.

6. The blinding strategy identified ‘wishful thinking’ amongst patients and RNs. Also, a small number of patients were not recruited because the surgeon decided against it. Both scenarios may be associated with a lack of equipoise that is either held by the surgeon or implied within the PIS. The approach to addressing surgeon equipoise is described above. Furthermore, it is proposed that the PIS is reviewed again by the Aintree Head & Neck Research Forum to look for unintentional bias towards the intervention.

7. This study has identified that the use of FS in ND may be associated with a learning effect. However, suboptimal data has prohibited formal identification and quantification. Therefore, a separate study is required prior to a definitive trial to address this. This learning effect data may then be used to set entry requirements for surgeons to participate in the definitive trial to ensure that they are in the asymptotic part of their learning curve when operating on trial participants. Furthermore, the outcomes used as performance proxies in this analysis need to be the same as in the definitive trial. This implies that this work should only be done once the work described in point 4 of this list have been addressed.

8. The addition of a 'forgot password' tab when logging in to reveal the allocation and a trial specific 'hotline' to the IT department are proposed. These will work to minimise the possibility of surgeons not revealing the allocation during surgery in a timely manner.

9. A future definitive trial will have considerably more data and would benefit from additional scheduled monitoring visits. Furthermore, using email alerts sent to the Trial Co-ordinator (TC) and PI regarding incomplete data may improve the accuracy of data recording.

9.2 Appropriateness of a Definitive DEFeND Trial

The findings of this REPT confirm that a definitive DEFeND trial in its current form is feasible from a methodological and intervention perspective. Recruitment data has shown that there are adequate numbers of patients who meet the eligibility criteria and are willing to be randomised. With the changes to the trial design and the pre-trial work summarised above, a definitive DEFeND trial would be well placed to answer the research question. Whilst the changes to the trial design can be implemented with immediate effect, the pre-trial work will be both extensive and time consuming. It is vitally important to learn from the weaknesses identified in the REPT

and address them systematically from first principles. In doing so, the proposed body of future work will provide important foundations for all HNS trials. Without laying these important foundations the shortcomings identified by this REPT could be repeated and progress.

Currently there is no published COS for HNS trials and addressing this unmet need should be the first priority. An important rationale for COS development is to ensure that trials report outcomes that are relevant to patients and other key stakeholders. Developing a COS for HNS trials will provide a useful structure to understand the priorities of patients. Examples exist from other research areas where patients have identified outcomes that are important to them that might not have otherwise been considered by healthcare professionals.(224-226)

Following the development of a HNS COS, the next steps should involve identification of the best instruments available to measure each core outcome. This would require a systematic review of all existing and relevant outcomes. This REPT has demonstrated a dearth of HNS specific outcomes so it is very possible that certain core outcomes will not have suitable instruments. Under these circumstances the development and validation of novel instruments should be the next priority. It has been suggested that reliance on clinical outcome measures (e.g. presence of disease, length of stay, re-admission rates) only provides a partial view of a patient's experience of healthcare because information on domains like pain, fatigue and degree of symptom bother are missing.(227) A well-developed and validated PROM has the potential to unlock a much more holistic evaluation of an intervention. For example, PROMs enable patients to assess whether their experience of treatment aligns with their expectations and may highlight areas of unmet need. One of the problems with using ClinROMs (e.g. Clavien-Dindo classification) is that they do not define when an outcome becomes significant for an individual patient. This is because the threshold for significance will vary between patients. Using ClinROMs in clinical trials requires investigators to decide the threshold on behalf of all patients (e.g. complications that are Clavien-Dindo grade IIIB or above). The WHQ validation work for the 'Bluebelle study' has shown it is possible to merge humanistic and complication outcomes by developing an instrument that can effectively diagnose SSI by patient report.(149)

The development of a COS for HNS trials and subsequent identification, development and validation of appropriate instruments is an important priority for all future HNS trials. It requires an extensive body of work that may take several years to complete. At that point in the future the research question pertaining to the role of FS in ND may no longer be important. Further evidence or the development of novel interventions and techniques may render this research obsolete. If understanding the role of FS in ND is still considered important, it would be prudent to update the systematic review presented in Chapter 2.

This REPT highlighted the need for identifying and quantifying the learning effect associated with FS in ND. However, it is important to wait until the COS for HNS has been developed and the appropriate instruments are in place before undertaking this research. Afterall. these instruments will form the basis of the performance proxies used to quantify the learning effect. Further qualitative research to identify and overcome barriers, reduce clinical workload associated with the trial, identify the need for extra training and protect research time will also be required at this stage. Only once this work has been completed can one really make an informed decision regarding the appropriateness of a definitive trial.

Chapter 10. CONCLUSIONS

The DEFeND REPT has demonstrated that a definitive trial is feasible and that many components of the trial design have worked well together. The proposed changes have the potential to improve this even further. Whilst the evaluation of clinical outcomes measured in this REPT have favoured FS, the effect sizes have been small. The proposed path to a definitive DEFeND trial is certainly long and one needs to consider the small effect sizes when starting this journey. Ultimately the methodological work relating to COS development and the instruments with which to measure each of them by is more urgent and has far reaching benefits beyond the definitive DEFeND trial. How the intervention performs within a definitive trial is highly dependent on the choice of primary outcome. If the findings of the trial are to influence policy and practice, then the chosen primary outcome needs to be relevant to patients. If we are to focus on what matters to patients, then they must be involved in determining which outcomes to measure and developing a COS for HNS trials is an important first step in this process.

REFRENCES

1. UK CR. Head & Neck Cancer Statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers.
2. McCarthy CE, Field JK, Rajlawat BP, Field AE, Marcus MW. Trends and regional variation in the incidence of head and neck cancers in England: 2002 to 2011. Int J Oncol. 2015;47(1):204-10.
3. Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, et al. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. Cancer Res. 2016;76(22):6598-606.
4. Ferlito A, Rinaldo A, Robbins KT, Leemans CR, Shah JP, Shaha AR, et al. Changing concepts in the surgical management of the cervical node metastasis. Oral Oncol. 2003;39(5):429-35.
5. Myers EN, Fagan JJ. Treatment of the N+ neck in squamous cell carcinoma of the upper aerodigestive tract. Otolaryngol Clin North Am. 1998;31(4):671-86.
6. Shaw RJ, Lowe D, Woolgar JA, Brown JS, Vaughan ED, Evans C, et al. Extracapsular spread in oral squamous cell carcinoma. Head Neck. 2010;32(6):714-22.
7. Crile GW. On the surgical treatment of cancer of the head and neck. With a summary of one hundred and twenty-one operations performed upon one hundred and ?ve patients. Transactions of the Southern Surgical and Gynecological Associations. 1905;18:108-27.
8. Ferlito A, Robbins KT, Rinaldo A. Neck dissection: historical perspective. J Laryngol Otol. 2004;118(6):403-5.
9. Price G RM, Wight R, Putnam G, Watson M. Major surgical resections in England: head and neck cancers. National Cancer Intelligence Network: Oxford Cancer Intelligence Unit; 2011.
10. Kerawala CJ, Heliotos M. Prevention of complications in neck dissection. Head Neck Oncol. 2009;1:35.
11. Bhushan SN AH. Management of neck dissection complications in head and neck cancers. International Surgery Journal. 2019;6(3):664-8.
12. Delaney SW, Shi H, Shokrani A, Sinha UK. Management of Chyle Leak after Head and Neck Surgery: Review of Current Treatment Strategies. Int J Otolaryngol. 2017;2017:8362874.
13. Dedivitis RA, Guimaraes AV, Pfuetzenreiter EG, Jr., Castro MA. [Neck dissection complications]. Braz J Otorhinolaryngol. 2011;77(1):65-9.
14. Shah S, Har-El G, Rosenfeld RM. Short-term and long-term quality of life after neck dissection. Head Neck. 2001;23(11):954-61.

15. Batstone MD, Scott B, Lowe D, Rogers SN. Marginal mandibular nerve injury during neck dissection and its impact on patient perception of appearance. Head Neck. 2009;31(5):673-8.
16. Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG, et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med. 2016;374(15):1444-54.
17. Main BG, McNair AGK, Haworth S, Rooshenas L, Hughes CW, Tierney P, et al. Core information set for informed consent to surgery for oral or oropharyngeal cancer: A mixed-methods study. Clin Otolaryngol. 2018;43(2):624-31.
18. Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res. 2010;89(3):219-29.
19. Jacobson L. K. JMB, Dedhia R. D., Niknam-Bienia S., Wong A.K. Impaired wound healing after radiation therapy: A systematic review of pathogenesis and treatment. JPRAS Opren. 2017;13:92-105.
20. International Surgical Outcomes Study g. Prospective observational cohort study on grading the severity of postoperative complications in global surgery research. Br J Surg. 2019;106(2):e73-e80.
21. Dell-Kuster S, Gomes NV, Gawria L, Aghlmandi S, Aduse-Poku M, Bissett I, et al. Prospective validation of classification of intraoperative adverse events (ClassIntra): international, multicentre cohort study. BMJ. 2020;370:m2917.
22. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery. 1992;111(5):518-26.
23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
24. Camino Willhuber G, Elizondo C, Slullitel P. Analysis of Postoperative Complications in Spinal Surgery, Hospital Length of Stay, and Unplanned Readmission: Application of Dindo-Clavien Classification to Spine Surgery. Global Spine J. 2019;9(3):279-86.
25. Hebert M, Cartier R, Dagenais F, Langlois Y, Coutu M, Noiseux N, et al. Standardizing Postoperative Complications-Validating the Clavien-Dindo Complications Classification in Cardiac Surgery. Semin Thorac Cardiovasc Surg. 2021;33(2):443-51.
26. van Wingerden JJ, Beets MR, Oostrom CA, Wever CF, Theuvenet WJ. The Clavien-Dindo classification for post-discharge reconstructive surgery complications and comparison of caregiver registration. J Plast Reconstr Aesthet Surg. 2019;72(8):1418-33.
27. Watt J, Tricco AC, Talbot-Hamon C, Pham B, Rios P, Grudniewicz A, et al. Identifying older adults at risk of harm following elective surgery: a systematic review and meta-analysis. BMC Med. 2018;16(1):2.
28. Goldstein DP, Sklar MC, de Almeida JR, Gilbert R, Gullane P, Irish J, et al. Frailty as a predictor of outcomes in patients undergoing head and neck cancer surgery. Laryngoscope. 2020;130(5):E340-E5.

29. Fu TS, Sklar M, Cohen M, de Almeida JR, Sawka AM, Alibhai SMH, et al. Is Frailty Associated With Worse Outcomes After Head and Neck Surgery? A Narrative Review. Laryngoscope. 2020;130(6):1436-42.
30. Pellini R, Mercante G, Marchese C, Terenzi V, Sperduti I, Manciocco V, et al. Predictive factors for postoperative wound complications after neck dissection. Acta Otorhinolaryngol Ital. 2013;33(1):16-22.
31. Malgonde MS KM. Complications after neck dissection. Medical Journal of Dr DY Patil Vidyapeeth. 2015;8(4):458-62.
32. Hutchison IL, Ridout F, Cheung SMY, Shah N, Hardee P, Surwald C, et al. Nationwide randomised trial evaluating elective neck dissection for early stage oral cancer (SEND study) with meta-analysis and concurrent real-world cohort. Br J Cancer. 2019;121(10):827-36.
33. Guo CB, Feng Z, Zhang JG, Peng X, Cai ZG, Mao C, et al. Supraomohyoid neck dissection and modified radical neck dissection for clinically node-negative oral squamous cell carcinoma: a prospective study of prognosis, complications and quality of life. J Craniomaxillofac Surg. 2014;42(8):1885-90.
34. Johnson JT, Cummings CW. Hematoma after head and neck surgery--a major complication? Otolaryngology. 1978;86(2):ORL171-5.
35. Williams J, Toews D, Prince M. Survey of the use of suction drains in head and neck surgery and analysis of their biomechanical properties. J Otolaryngol. 2003;32(1):16-22.
36. Hemmat SM, Wang SJ, Ryan WR. Neck Dissection Technique Commonality and Variance: A Survey on Neck Dissection Technique Preferences among Head and Neck Oncologic Surgeons in the American Head and Neck Society. Int Arch Otorhinolaryngol. 2017;21(1):8-16.
37. Woods RS, Woods JF, Duignan ES, Timon C. Systematic review and meta-analysis of wound drains after thyroid surgery. Br J Surg. 2014;101(5):446-56.
38. Batstone MD, Lowe D, Shaw RJ, Brown JS, Vaughan ED, Rogers SN. Passive versus active drainage following neck dissection: a non-randomised prospective study. Eur Arch Otorhinolaryngol. 2009;266(1):121-4.
39. Phillips BT, Wang ED, Mirrer J, Lanier ST, Khan SU, Dagum AB, et al. Current practice among plastic surgeons of antibiotic prophylaxis and closed-suction drains in breast reconstruction: experience, evidence, and implications for postoperative care. Ann Plast Surg. 2011;66(5):460-5.
40. Meyerson JM. A Brief History of Two Common Surgical Drains. Ann Plast Surg. 2016;77(1):4-5.
41. Flam JO, Smith RV. What is the optimal time for removing drains in uncomplicated head and neck surgery? Laryngoscope. 2018;128(3):545-6.
42. Harris T, Doolarkhan Z, Fagan JJ. Timing of removal of neck drains following head and neck surgery. Ear Nose Throat J. 2011;90(4):186-9.
43. Tamplen ML, Tamplen J, Shuman E, Heaton CM, George JR, Wang SJ, et al. Comparison of Output Volume Thresholds for Drain Removal After Selective Lateral Neck Dissection: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2017;143(12):1195-9.

44. Kasbekar AV, Davies F, Upile N, Ho MW, Roland NJ. The management of vacuum neck drains in head and neck surgery and the comparison of two different practice protocols for drain removal. Ann R Coll Surg Engl. 2016;98(1):53-5.
45. Jackson MR. Fibrin sealants in surgical practice: An overview. Am J Surg. 2001;182(2 Suppl):1S-7S.
46. Edwards SJ, Crawford F, van Velthoven MH, Berardi A, Osei-Assibey G, Bacelar M, et al. The use of fibrin sealant during non-emergency surgery: a systematic review of evidence of benefits and harms. Health Technol Assess. 2016;20(94):1-224.
47. Morikawa T. Tissue sealing. Am J Surg. 2001;182(2 Suppl):29S-35S.
48. Fibrin Sealant Market Size, Share & Industry Analysis Fortune Business Insights2018 [Available from: https://www.fortunebusinessinsights.com/industry-reports/fibrin-sealants-market-100316.
49. Surgical Care: Baxter Healthcare LTD; [Available from: https://www.baxterhealthcare.co.uk/healthcare-professionals/surgical-care.
50. EVICEL Fibrin Sealant, 2010: Johnson & Johnson; [Available from: https://ourstory.jnj.com/evicel-fibrin-sealant.
51. LTD BH. ARTISS Solutions for Sealant: SmPC 2019 [Available from: https://www.medicines.org.uk/emc/product/1800/smpc.
52. Bergel S. Uber Wirkungen des Fibrins. Deutsche Medizinische Wochenschrift 1909;35.
53. Cronkite E.P. LEL, Deaver J.M. Use of Thrombin and Fibrinogen in skin grafting: preliminary report. JAMA. 1944;124(14):976 - 8.
54. Mintz PD, Mayers L, Avery N, Flanagan HL, Burks SG, Spotnitz WD. Fibrin sealant: clinical use and the development of the University of Virginia Tissue Adhesive Center. Ann Clin Lab Sci. 2001;31(1):108-18.
55. Spotnitz WD. Commercial fibrin sealants in surgical care. Am J Surg. 2001;182(2 Suppl):8S-14S.
56. Matras H, Dinges HP, Lassmann H, Mamoli B. [Suture-free interfascicular nerve transplantation in animal experiments]. Wien Med Wochenschr. 1972;122(37):517-23.
57. Matras H, Braun F, Lassmann H, Ammerer HP, Mamoli B. Plasma clot welding of nerves. (Experimental report). J Maxillofac Surg. 1973;1(4):236-47.
58. FDA. TISSEEL 2018 [Available from: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/tisseel.
59. Agency MaHPR. Sprayable fibrin sealants (Evicel, Tisseel and Artiss): updated guidance 2014 [Available from: https://www.gov.uk/drug-safety-update/sprayable-fibrin-sealants-evicel-tisseel-and-artiss-updated-guidance.
60. Agency EM. Evicel: EPAR - Product Information 2020 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/evicel.
61. Ltd BH. TISSEEL Ready to use Solutions for Sealant 2020 [Available from: https://www.medicines.org.uk/emc/product/1801/smpc#gref.
62. Ltd BH. ARTISS Solution for Sealant 2018 [Available from: https://www.medicines.org.uk/emc/product/1800/smpc#gref.

63. Reiner AP. Fibrin glue increasingly popular for topical surgical haemostasis. Laboratory Medicine. 1999;30(3).
64. Carton J, Daly R, Ramani P. Clinical pathology. Oxford: Oxford University Press; 2006.
65. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):15-31.
66. Martinowitz U, Schulman S. Fibrin sealant in surgery of patients with a hemorrhagic diathesis. Thromb Haemost. 1995;74(1):486-92.
67. Milic DJ, Perisic ZD, Zivic SS, Stanojkovic ZA, Stojkovic AM, Karanovic ND, et al. Prevention of pocket related complications with fibrin sealant in patients undergoing pacemaker implantation who are receiving anticoagulant treatment. Europace. 2005;7(4):374-9.
68. Bodner L, Weinstein JM, Baumgarten AK. Efficacy of fibrin sealant in patients on various levels of oral anticoagulant undergoing oral surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86(4):421-4.
69. Karimi M, Peyvandi F, Naderi M, Shapiro A. Factor XIII deficiency diagnosis: Challenges and tools. Int J Lab Hematol. 2018;40(1):3-11.
70. Dickneite G, Metzner HJ, Kroez M, Hein B, Nicolay U. The importance of factor XIII as a component of fibrin sealants. J Surg Res. 2002;107(2):186-95.
71. CSL B. Beriplast P combi-set 2012 [Available from: http://mri.cts-mrp.eu/download/DE_H_0135_003_FinalLabelling_3of3.pdf.
72. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc. 2015;13(3):196-207.
73. van Akkooi AC, Bouwhuis MG, van Geel AN, Hoedemaker R, Verhoef C, Grunhagen DJ, et al. Morbidity and prognosis after therapeutic lymph node dissections for malignant melanoma. Eur J Surg Oncol. 2007;33(1):102-8.
74. Weldrick C, Bashar K, O'Sullivan TA, Gillis E, Clarke Moloney M, Tang TY, et al. A comparison of fibrin sealant versus standard closure in the reduction of postoperative morbidity after groin dissection: A systematic review and meta-analysis. Eur J Surg Oncol. 2014;40(11):1391-8.
75. Sajid MS, Hutson KH, Rapisarda IF, Bonomi R. Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery. Cochrane Database Syst Rev. 2013(5):CD009557.
76. Takeshima N, Sozu T, Tajika A, Ogawa Y, Hayasaka Y, Furukawa TA. Which is more generalizable, powerful and interpretable in meta-analyses, mean difference or standardized mean difference? BMC Med Res Methodol. 2014;14:30.
77. Dhillon S. Fibrin sealant (evicel(R) [quixil(R)/crosseal]): a review of its use as supportive treatment for haemostasis in surgery. Drugs. 2011;71(14):1893-915.
78. Benevento R, Santoriello A, Pellino G, Sciaudone G, Candilio G, De Fatico GS, et al. The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node

dissection for breast cancer. A randomized controlled trial. Int J Surg. 2014;12(11):1210-5.
79. Hester TR, Jr., Shire JR, Nguyen DB, Gerut ZE, Chen AH, Diamond J, et al. Randomized, controlled, phase 3 study to evaluate the safety and efficacy of fibrin sealant VH S/D 4 s-apr (Artiss) to improve tissue adherence in subjects undergoing rhytidectomy. Aesthet Surg J. 2013;33(4):487-96.
80. Pilone V, Vitiello A, Borriello C, Gargiulo S, Forestieri P. The use of a fibrin glue with a low concentration of thrombin decreases seroma formation in postbariatric patients undergoing circular abdominoplasty. Obes Surg. 2015;25(2):354-9.
81. Foster K, Greenhalgh D, Gamelli RL, Mozingo D, Gibran N, Neumeister M, et al. Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. J Burn Care Res. 2008;29(2):293-303.
82. Bajwa MS, Tudur-Smith C, Shaw RJ, Schache AG. Fibrin sealants in soft tissue surgery of the head and neck: A systematic review and meta-analysis of randomised controlled trials. Clin Otolaryngol. 2017;42(6):1141-52.
83. Por YC, Shi L, Samuel M, Song C, Yeow VK. Use of tissue sealants in face-lifts: a metaanalysis. Aesthetic Plast Surg. 2009;33(3):336-9.
84. Killion EA, Hyman CH, Hatef DA, Hollier LH, Jr., Reisman NR. A systematic examination of the effect of tissue glues on rhytidectomy complications. Aesthet Surg J. 2015;35(3):229-34.
85. Sproat R, Radford P, Hunt A. Hemostatic glues in tonsillectomy: A systematic review. Laryngoscope. 2016;126(1):236-42.
86. Bajwa MS SA, Shaw RJ, Tudur-Smith C, Rey P. Fibrin tissue adhesives for wound healing in soft-tissue surgery of the head and neck. PROSPERO: International Prospective Register of Systematic Reviews. 2016;CRD42016036766:http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036766.
87. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
88. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0. http://cochrane-handbook.org/: The Cochrane Collaboration: Copenhagen; Updated March 2011.
89. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
90. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
91. Hornig JD GM, Lentsch EJ, Fuller CW, Condrey J, Nguyen SA. Fibrin sealant use in thyroidectomy: A prospective, randomized, placebo-controlled double blind trial using EVICEL. Otorhinolaryngology- Head and Neck Surgery. 2016;1(1):21-4.
92. Uwiera TC, Uwiera RR, Seikaly H, Harris JR. Tisseel and its effects on wound drainage post-thyroidectomy: prospective, randomized, blinded, controlled study. J Otolaryngol. 2005;34(6):374-8.

93. Kim TW, Choi SY, Jang MS, Lee GG, Nam ME, Son YI, et al. Efficacy of fibrin sealant for drainage reduction in total thyroidectomy with bilateral central neck dissection. Otolaryngol Head Neck Surg. 2012;147(4):654-60.
94. Vidal-Perez O, Flores-Siguenza L, Valentini M, Astudillo-Pombo E, Fernandez-Cruz L, Garcia-Valdecasas JC. [Application of fibrin sealant in patients operated on for differentiated thyroid cancer. What do we improve?]. Cir Cir. 2016;84(4):282-7.
95. Huang CW, Wang CC, Jiang RS, Huang YC, Ho HC, Liu SA. The impact of tissue glue in wound healing of head and neck patients undergoing neck dissection. Eur Arch Otorhinolaryngol. 2016;273(1):245-50.
96. Maharaj M, Diamond C, Williams D, Seikaly H, Harris J. Tisseel to reduce postparotidectomy wound drainage: randomized, prospective, controlled trial. J Otolaryngol. 2006;35(1):36-9.
97. Hester TR, Jr., Gerut ZE, Shire JR, Nguyen DB, Chen AH, Diamond J, et al. Exploratory, randomized, controlled, phase 2 study to evaluate the safety and efficacy of adjuvant fibrin sealant VH S/D 4 S-Apr (ARTISS) in patients undergoing rhytidectomy. Aesthet Surg J. 2013;33(3):323-33.
98. Lee S, Pham AM, Pryor SG, Tollefson T, Sykes JM. Efficacy of Crosseal fibrin sealant (human) in rhytidectomy. Arch Facial Plast Surg. 2009;11(1):29-33.
99. Marchac D, Greensmith AL. Early postoperative efficacy of fibrin glue in face lifts: a prospective randomized trial. Plast Reconstr Surg. 2005;115(3):911-6; discussion 7-8.
100. Oliver DW, Hamilton SA, Figle AA, Wood SH, Lamberty BG. A prospective, randomized, double-blind trial of the use of fibrin sealant for face lifts. Plast Reconstr Surg. 2001;108(7):2101-5, discussion 6-7.
101. Mushi E, Kinshuck A, Svecova N, Schache A, Jones TM, Tandon S, et al. The use of Tisseel fibrin sealant in selective neck dissection--a retrospective study in a tertiary Head and Neck Surgery centre. Clin Otolaryngol. 2015;40(2):93-7.
102. Yoo J, Chandarana S, Fung K, Franklin JH, Nichols AC, Doyle PC. The use of autologous platelet and plasma products in salvage neck dissections: a prospective clinical study evaluating early and late wound healing. J Biol Regul Homeost Agents. 2012;26(2 Suppl 1):63S-9S.
103. Earnshaw CH, Kinshuck AJ, Loh C, Tandon S, Jackson SR, Jones TM, et al. An audit of fifty patients receiving Artiss fibrin sealant in lateral selective neck dissections. Clin Otolaryngol. 2020;45(2):264-7.
104. Conboy P, Brown DH. Use of tissue sealant for day surgery parotidectomy. J Otolaryngol Head Neck Surg. 2008;37(2):208-11.
105. Kaur G, Hutchison I, Mehanna H, Williamson P, Shaw R, Tudur Smith C. Barriers to recruitment for surgical trials in head and neck oncology: a survey of trial investigators. BMJ Open. 2013;3(4).
106. Olson E, Wintheiser G, Wolfe KM, Droessler J, Silberstein PT. Epidemiology of Thyroid Cancer: A Review of the National Cancer Database, 2000-2013. Cureus. 2019;11(2):e4127.
107. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis. 1967;20(8):637-48.

108. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ. 2008;337:a2390.
109. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
110. Blencowe NS, Mills N, Cook JA, Donovan JL, Rogers CA, Whiting P, et al. Standardizing and monitoring the delivery of surgical interventions in randomized clinical trials. Br J Surg. 2016;103(10):1377-84.
111. Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials. 2009;10:37.
112. Zwarenstein M. 'Pragmatic' and 'explanatory' attitudes to randomised trials. J R Soc Med. 2017;110(5):208-18.
113. Chapman SJ, Shelton B, Mahmood H, Fitzgerald JE, Harrison EM, Bhangu A. Discontinuation and non-publication of surgical randomised controlled trials: observational study. BMJ. 2014;349:g6870.
114. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454-63.
115. Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. Trials. 2009;10(1):9.
116. Buxton MJ. Problems in the economic appraisal of new health technology: the evaluation of heart transplants in the uk. In: Drummond MF, editor. Economic appraisal of health technology in the European Community: Oxford: Oxford Medical; 1987. p. 103-18.
117. NIHR. Glossary 2020 [Available from: www.nihr.ac.uk/glossary?letter=P&postcategory=-1.
118. NIHR. Glossary 2020 [Available from: https://www.nihr.ac.uk/glossary?letter=F&postcategory=-1.
119. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PLoS One. 2016;11(3):e0150205.
120. Blatch-Jones AJ, Pek W, Kirkpatrick E, Ashton-Key M. Role of feasibility and pilot studies in randomised controlled trials: a cross-sectional study. BMJ Open. 2018;8(9):e022233.
121. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374(9683):86-9.
122. Blencowe NS, Cook JA, Pinkney T, Rogers C, Reeves BC, Blazeby JM. Delivering successful randomized controlled trials in surgery: Methods to optimize collaboration and study design. Clin Trials. 2017;14(2):211-8.
123. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. BMJ. 2002;324(7351):1448-51.
124. Fairhurst K, Blazeby JM, Potter S, Gamble C, Rowlands C, Avery KNL. Value of surgical pilot and feasibility study protocols. Br J Surg. 2019;106(8):968-78.
125. The Collaboration: The IDEAL Collaboration; [Available from: http://www.ideal-collaboration.net/the-collaboration/.

126. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.
127. Hirst A, Philippou Y, Blazeby J, Campbell B, Campbell M, Feinberg J, et al. No Surgical Innovation Without Evaluation: Evolution and Further Development of the IDEAL Framework and Recommendations. Ann Surg. 2019;269(2):211-20.
128. Rooshenas L, Elliott D, Wade J, Jepson M, Paramasivan S, Strong S, et al. Conveying Equipoise during Recruitment for Clinical Trials: Qualitative Synthesis of Clinicians' Practices across Six Randomised Controlled Trials. PLoS Med. 2016;13(10):e1002147.
129. Dal-Re R, Janiaud P, Ioannidis JPA. Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC Med. 2018;16(1):49.
130. Kim JT, Kim YH, Kim SW. Effect of fibrin sealant in positioning and stabilizing microvascular pedicle: A comparative study. Microsurgery. 2017;37(5):406-9.
131. Beltramini GA, Rabbiosi D, Allevi F, Gianni AB, Biglioli F. The use of fibrin glue to stabilize geometry of free-flaps vascular pedicle. Oral Maxillofac Surg. 2018;22(1):113-4.
132. Hazari A, Walton P. The UK National Flap Registry (UKNFR): A National Database for all pedicled and free flaps in the UK. J Plast Reconstr Aesthet Surg. 2015;68(12):1633-6.
133. Halloran CM, Platt K, Gerard A, Polydoros F, O'Reilly DA, Gomez D, et al. PANasta Trial; Cattell Warren versus Blumgart techniques of panreatico-jejunostomy following pancreato-duodenectomy: Study protocol for a randomized controlled trial. Trials. 2016;17:30.
134. Maillard J, Elia N, Haller CS, Delhumeau C, Walder B. Preoperative and early postoperative quality of life after major surgery - a prospective observational study. Health Qual Life Outcomes. 2015;13:12.
135. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg. 2014;259(5):916-23.
136. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol. 2003;21(3):555-63.
137. Monteiro E, Sklar MC, Eskander A, de Almeida JR, Shrime M, Gullane P, et al. Assessment of the Clavien-Dindo classification system for complications in head and neck surgery. Laryngoscope. 2014;124(12):2726-31.
138. Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. Trials. 2009;10:9.
139. Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ Open. 2017;7(2):e013537.

140. Surgical Trials Centres: Royal College of Surgeons of England; [Available from: https://www.rcseng.ac.uk/standards-and-research/research/surgical-trials-initiative/surgical-trials-centres/.
141. Why Should I Register and Submit Results: ClinicalTrials.gov; [Available from: https://clinicaltrials.gov/ct2/manage-recs/background.
142. Why register: ISRCTN Registry; [Available from: https://www.isrctn.com/page/why-register.
143. Adams M, Caffrey L, McKevitt C. Barriers and opportunities for enhancing patient recruitment and retention in clinical research: findings from an interview study in an NHS academic health science centre. Health Res Policy Syst. 2015;13:8.
144. Isaksson E, Wester P, Laska AC, Nasman P, Lundstrom E. Identifying important barriers to recruitment of patients in randomised clinical studies using a questionnaire for study personnel. Trials. 2019;20(1):618.
145. Bellary S, Krishnankutty B, Latha MS. Basics of case report form designing in clinical research. Perspect Clin Res. 2014;5(4):159-66.
146. MACRO Advanced data collection for clinical research: Elsevier; [Available from: https://www.elsevier.com/en-gb/solutions/veridata/macro.
147. Taylor RJ, Chepeha JC, Teknos TN, Bradford CR, Sharma PK, Terrell JE, et al. Development and validation of the neck dissection impairment index: a quality of life measure. Arch Otolaryngol Head Neck Surg. 2002;128(1):44-9.
148. Divi V, Harris J, Harari PM, Cooper JS, McHugh J, Bell D, et al. Establishing quality indicators for neck dissection: Correlating the number of lymph nodes with oncologic outcomes (NRG Oncology RTOG 9501 and RTOG 0234). Cancer. 2016;122(22):3464-71.
149. Bluebelle Study G. Validation of the Bluebelle Wound Healing Questionnaire for assessment of surgical-site infection in closed primary wounds after hospital discharge. Br J Surg. 2019;106(3):226-35.
150. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain. 2003;4(7):407-14.
151. Templates for supporting documents: Integrated Research Application System; [Available from: https://www.myresearchproject.org.uk/help/hlptemplatesfor.aspx#Contracts-Agreements.
152. Attributing the costs of health and social care research: Deapartment of Health and Social Care; 2012 [Available from: https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research.
153. Bajwa MS, Carruthers S, Hanson R, Jackson R, Braithwaite C, Edwards M, et al. Determining the effectiveness of fibrin sealants in reducing complications in patients undergoing lateral neck dissection (DEFeND): study protocol for a randomised external pilot trial. Pilot Feasibility Stud. 2020;6:76.
154. Ebrahimi A, Clark JR, Amit M, Yen TC, Liao CT, Kowalski LP, et al. Minimum nodal yield in oral squamous cell carcinoma: defining the standard of care in a

multicenter international pooled validation study. Ann Surg Oncol. 2014;21(9):3049-55.
155. Divi V, Chen MM, Nussenbaum B, Rhoads KF, Sirjani DB, Holsinger FC, et al. Lymph Node Count From Neck Dissection Predicts Mortality in Head and Neck Cancer. J Clin Oncol. 2016;34(32):3892-7.
156. Mehanna H, Evans M, Beasley M, Chatterjee S, Dilkes M, Homer J, et al. Oropharyngeal cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S90-S6.
157. Kerawala C, Roques T, Jeannon JP, Bisase B. Oral cavity and lip cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S83-S9.
158. Jones TM, De M, Foran B, Harrington K, Mortimore S. Laryngeal cancer: United Kingdom National Multidisciplinary guidelines. J Laryngol Otol. 2016;130(S2):S75-S82.
159. Sood S, McGurk M, Vaz F. Management of Salivary Gland Tumours: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S142-S9.
160. Newlands C, Currie R, Memon A, Whitaker S, Woolford T. Non-melanoma skin cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S125-S32.
161. Good Practice in Research and Consent to Research: General Medical Council; 2020 [Available from: https://www.gmc-uk.org/-/media/documents/Good_practice_in_research_and_consent_to_research.pdf_58834843.pdf.
162. 0 - 18 years: guidance for all doctors: General Medical Council; 2018 [Available from: https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/0-18-years.
163. Dietrich W, Ebell A, Busley R, Boulesteix AL. Aprotinin and anaphylaxis: analysis of 12,403 exposures to aprotinin in cardiac surgery. Ann Thorac Surg. 2007;84(4):1144-50.
164. Woods RK, Stoney RM, Raven J, Walters EH, Abramson M, Thien FC. Reported adverse food reactions overestimate true food allergy in the community. Eur J Clin Nutr. 2002;56(1):31-6.
165. Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T, et al. Prevalence of adverse reactions to food in Germany - a population study. Allergy. 2004;59(3):338-45.
166. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol. 1999;52(1):19-26.
167. Group. SHoTSWEGaW. Annual SHOT report. 2017.
168. Foster JD, Mackenzie H, Nelson H, Hanna GB, Francis NK. Methods of quality assurance in multicenter trials in laparoscopic colorectal surgery: a systematic review. Ann Surg. 2014;260(2):220-9.
169. Annual Report: National Institute of Health Research; 2019/20 [Available from: https://www.nihr.ac.uk/documents/about-us/our-contribution-to-research/research-performance/NIHR_Annual_Report_19_20.pdf.
170. Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised

controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open. 2017;7(3):e015276.
171. Arandjelovic O. A new framework for interpreting the outcomes of imperfectly blinded controlled clinical trials. PLoS One. 2012;7(12):e48984.
172. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study. Stat Med. 1996;15(13):1421-34.
173. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials. 2004;25(2):143-56.
174. Kolahi J, Bang H, Park J. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. Community Dent Oral Epidemiol. 2009;37(6):477-84.
175. Desbiens NA. In randomized controlled trials, should subjects in both placebo and drug groups be expected to guess that they are taking drug 50% of the time? Med Hypotheses. 2002;59(3):227-32.
176. Braun V, Clarke V. Successful qualitative research : a practical guide for beginners. London: SAGE; 2013.
177. Cook JA, Ramsay CR, Fayers P. Statistical evaluation of learning curve effects in surgical trials. Clin Trials. 2004;1(5):421-7.
178. Conroy EJ, Rosala-Hallas A, Blazeby JM, Burnside G, Cook JA, Gamble C. Randomized trials involving surgery did not routinely report considerations of learning and clustering effects. J Clin Epidemiol. 2019;107:27-35.
179. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, et al. Challenges in evaluating surgical innovation. Lancet. 2009;374(9695):1097-104.
180. Khan N, Abboudi H, Khan MS, Dasgupta P, Ahmed K. Measuring the surgical 'learning curve': methods, variables and competency. BJU Int. 2014;113(3):504-8.
181. Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT. Statistical assessment of the learning curves of health technologies. Health Technol Assess. 2001;5(12):1-79.
182. Papachristofi O, Jenkins D, Sharples LD. Assessment of learning curves in complex surgical interventions: a consecutive case-series study. Trials. 2016;17(1):266.
183. Agency EM. Data Monitoring Committees. 2005.
184. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
185. COMET. COMET Initiative 2020 [Available from: www.comet-initiative.org.
186. Xue Z, Sun J, Li T, Huang Z, Chen W. How to evaluate the clinical outcome of joint-preserving treatment for osteonecrosis of the femoral head: development of a core outcome set. J Orthop Surg Res. 2019;14(1):317.
187. van der Poel HG, Wit EM, Acar C, van den Berg NS, van Leeuwen FWB, Valdes Olmos RA, et al. Sentinel node biopsy for prostate cancer: report from a consensus panel meeting. BJU Int. 2017;120(2):204-11.

188. MacLennan S, Williamson PR, Bekema H, Campbell M, Ramsay C, N'Dow J, et al. A core outcome set for localised prostate cancer effectiveness trials. BJU Int. 2017;120(5B):E64-E79.
189. Ingoe HMA, Eardley W, Rangan A, Hewitt C, McDaid C. An international multi-stakeholder delphi consensus exercise to develop a core outcomes set (COS) for surgical fixation of rib fractures. Injury. 2020;51(2):224-9.
190. Coulman KD, Hopkins J, Brookes ST, Chalmers K, Main B, Owen-Smith A, et al. A Core Outcome Set for the Benefits and Adverse Events of Bariatric and Metabolic Surgery: The BARIACT Project. PLoS Med. 2016;13(11):e1002187.
191. Leo DG, Jones H, Murphy R, Leong JW, Gambling T, Long AF, et al. The outcomes of Perthes' disease. Bone Joint J. 2020;102-B(5):611-7.
192. Sherratt FC, Allin BSR, Kirkham JJ, Walker E, Young B, Wood W, et al. Core outcome set for uncomplicated acute appendicitis in children and young people. Br J Surg. 2020;107(8):1013-22.
193. Sahnan K, Tozer PJ, Adegbola SO, Lee MJ, Heywood N, McNair AGK, et al. Developing a core outcome set for fistulising perianal Crohn's disease. Gut. 2019;68(2):226-38.
194. Srikandarajah N, Noble A, Clark S, Wilby M, Freeman BJC, Fehlings MG, et al. Cauda Equina Syndrome Core Outcome Set (CESCOS): An international patient and healthcare professional consensus for research studies. PLoS One. 2020;15(1):e0225907.
195. Allin BSR, Bradnock T, Kenny S, Kurinczuk JJ, Walker G, Knight M, et al. NETS(1HD) study: development of a Hirschsprung's disease core outcome set. Arch Dis Child. 2017;102(12):1143-51.
196. van Tol RR, Kimman ML, Melenhorst J, Stassen LPS, Dirksen CD, Breukink SO, et al. European Society of Coloproctology Core Outcome Set for haemorrhoidal disease: an international Delphi study among healthcare professionals. Colorectal Dis. 2019;21(5):570-80.
197. Allin BSR, Hall NJ, Ross AR, Marven SS, Kurinczuk JJ, Knight M, et al. Development of a gastroschisis core outcome set. Arch Dis Child Fetal Neonatal Ed. 2019;104(1):F76-F82.
198. Feldman LS, Lee L, Fiore J, Jr. What outcomes are important in the assessment of Enhanced Recovery After Surgery (ERAS) pathways? Can J Anaesth. 2015;62(2):120-30.
199. Benstoem C, Moza A, Meybohm P, Stoppe C, Autschbach R, Devane D, et al. A core outcome set for adult cardiac surgery trials: A consensus study. PLoS One. 2017;12(11):e0186772.
200. Haywood KL, Griffin XL, Achten J, Costa ML. Developing a core outcome set for hip fracture trials. Bone Joint J. 2014;96-B(8):1016-23.
201. Potter S, Holcombe C, Ward JA, Blazeby JM, Group BS. Development of a core outcome set for research and audit studies in reconstructive breast surgery. Br J Surg. 2015;102(11):1360-71.

202. Avery KNL, Chalmers KA, Brookes ST, Blencowe NS, Coulman K, Whale K, et al. Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. Ann Surg. 2018;267(4):700-10.
203. Singh JA, Dohm M, Sprowson AP, Wall PD, Richards BL, Gossec L, et al. Outcome Domains and Measures in Total Joint Replacement Clinical Trials: Can We Harmonize Them? An OMERACT Collaborative Initiative. J Rheumatol. 2015;42(12):2496-502.
204. McNair AG, Whistance RN, Forsythe RO, Macefield R, Rees J, Pullyblank AM, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLoS Med. 2016;13(8):e1002071.
205. Ropka ME. Symptom status and functional status outcomes: humanistic outcomes in obesity disease management. Obes Res. 2002;10 Suppl 1:42S-9S.
206. Velentgas P, Dreyer NA, Wu AW. Outcome Definition and Measurement. In: Velentgas P, Dreyer NA, Nouriah P, editors. Developing a Protocol for Observational Comparative Effectiveness Research: A user's Guide: Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
207. Waters AM, Tudur Smith C, Young B, Jones TM. The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer. Trials. 2014;15:168.
208. Boyes H, Barraclough J, Ratansi R, Rogers SN, Kanatas A. Structured review of the patient-reported outcome instruments used in clinical trials in head and neck surgery. Br J Oral Maxillofac Surg. 2018;56(3):161-7.
209. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013;258(1):1-7.
210. Slankamenac K, Nederlof N, Pessaux P, de Jonge J, Wijnhoven BP, Breitenstein S, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg. 2014;260(5):757-62; discussion 62-3.
211. Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord. 2003;4:11.
212. Beaton DE, Wright JG, Katz JN, Upper Extremity Collaborative G. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg Am. 2005;87(5):1038-46.
213. Breckenridge JD, McAuley JH. Shoulder Pain and Disability Index (SPADI). J Physiother. 2011;57(3):197.
214. Hassan SJ, Weymuller EA, Jr. Assessment of quality of life in head and neck cancer patients. Head Neck. 1993;15(6):485-96.
215. Eden MM. Shoulder-Specific Patient Reported Outcome Measures for Use in Patients with Head and Neck Cancer:An Assessment of Reliability, Construct Validity, and Overall Appropriateness of Test Score Interpretation Using Rasch Analysis: Nova Southeastern University; 2018.

216. Parikh S, Tedman BM, Scott B, Lowe D, Rogers SN. A double blind randomised trial of IIb or not IIb neck dissections on electromyography, clinical examination, and questionnaire-based outcomes: a feasibility study. Br J Oral Maxillofac Surg. 2012;50(5):394-403.
217. Dziegielewski PT, McNeely ML, Ashworth N, O'Connell DA, Barber B, Courneya KS, et al. 2b or not 2b? Shoulder function after level 2b neck dissection: A double-blind randomized controlled clinical trial. Cancer. 2020;126(7):1492-501.
218. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149-60.
219. Boaz A, Hanney S, Jones T, Soper B. Does the engagement of clinicians and organisations in research improve healthcare performance: a three-stage review. BMJ Open. 2015;5(12):e009415.
220. Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. BMJ Open. 2012;2(1):e000496.
221. Cancer incidence for common cancers: Cancer Research UK; [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Zero.
222. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). Trials. 2016;17(1):283.
223. Horton R. Surgical research or comic opera: questions, but few answers. Lancet. 1996;347(9007):984-5.
224. Serrano-Aguilar P, Trujillo-Martin MM, Ramos-Goni JM, Mahtani-Chugani V, Perestelo-Perez L, Posada-de la Paz M. Patient involvement in health research: a contribution to a systematic review on the effectiveness of treatments for degenerative ataxias. Soc Sci Med. 2009;69(6):920-5.
225. Kirwan JR, Hewlett SE, Heiberg T, Hughes RA, Carr M, Hehir M, et al. Incorporating the patient perspective into outcome assessment in rheumatoid arthritis--progress at OMERACT 7. J Rheumatol. 2005;32(11):2250-6.
226. Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials. 2012;13:103.
227. Coulter A. Measuring what matters to patients. BMJ. 2017;356:j816.

APPENDICES

Appendix A. WORKING DOCUMENTS

A.1 Protocol

CONFIDENTIAL

Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

- **Study Sponsor:**

University of Liverpool Research Support Office

2nd Floor Block D Waterhouse Building 3 Brownlow Street

Liverpool L69 3GL

ISRCTN number:	99181100
IRAS number:	234851
Protocol version:	2.0
Date:	27-Jun-2018

- **General Information**

This document describes the DEFeND trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (North West Surgical Trials Centre (NWSTC) part of Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via NWSTC/LCTU.

- **Statement of Compliance**

- This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, NWSTC/LCTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

- **UK Registration**

- This study will have Health Research Authority (HRA) Approval. All research sites will confirm capacity and capability to conduct the study and will sign a Research Site Agreement.

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- **Glossary**

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
CI	Chief Investigator
CO2	Carbon Dioxide
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DOB	Date of Birth
(E)CRF	Electronic Case Report Form
FDA	United States Food & Drug Administration
FS	Fibrin Sealant
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
HRA	Health Research Authority
IB	Investigator's Brochure

ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ISRCTN	International Standard Randomised Controlled Trial Number
LCTU	Liverpool Cancer Trials Unit
LREC	Local Research Ethics Committee
MACRO	Data Capture & Management Software
MCID	Minimal Clinically Important Difference
MCRN CTU	Medicines for Children Clinical Trials Unit
MDT	Multidisciplinary Team
MHRA	Medicines and Health Products Regulatory Agency
MREC	Multi-centre Research Ethics Committee
NDII	Neck Dissection Impairment Index
NHS	National Health Service
NPSA	National Patient Safety Agency
NWSTC	North West Surgical Trials Centre

PI	Principal Investigator
PIS	Patient Information Sheet
R&D	Research & Development
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SOC	Standard of Care
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAME	Acute Toxicity, Adverse Late Effects and Mortality Risk Generated by a Treatment Programme
TARDIS	Treatment Allocation Randomisation System
TMG	Trial Monitoring Group

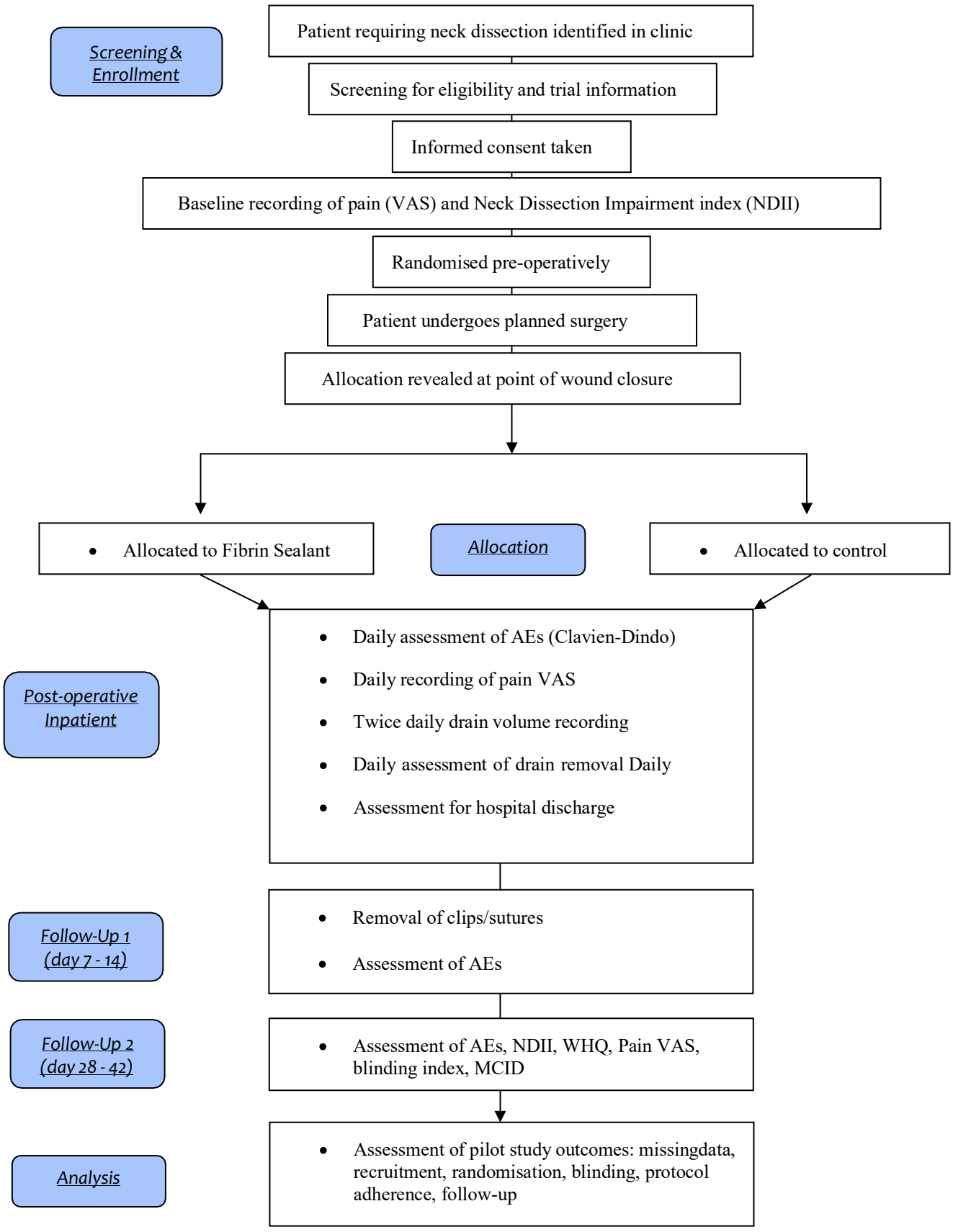
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UKCRN	United Kingdom Clinical Research Network
VAS	Visual Analogue Scale
WHQ	Bluebelle study Wound Healing Questionnaire

1 PROTOCOL SUMMARY

Title:	**Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial**
Phase:	Randomised External Pilot Trial
Sample Size:	A minimum of 50 patients (UK)
Main Inclusion Criteria:	• Patients due to undergo lateral neck dissection • Neck dissection to include a minimum of 3 levels • Patients who have capacity to consent
Main Exclusion Criteria:	• Age < 18 years • Bilateral neck dissection • Presence of a vascular pedicle for reconstruction • Pregnancy or breast feeding • Known hypersensitivity reaction to Aprotinin • Previous exposure to Fibrin Sealant within 6 months • Known allergy to dairy products

Number of Sites:	Aintree University Hospital, Liverpool UK Queen Victoria Hospital, East Grinstead UK
Study Duration:	12 Months
Description of Intervention:	Application of Artiss fibrin sealant (Baxter Healthcare LTD) to the surgical wound. Up to 2ml driven by medical air at 1.5 bar, minimum 10 cm away from wound prior to closure.
Objectives:	The main objectives of this study are to assess if a future phase III trial is feasible and to ensure the individual aspects of the trial design work well together. The key objectives of this randomised external pilot study are to assess the following points: • Whether patients can be recruited and retained at a rate of approximately 4 patients per month across the 2 centres. • Determining the effectiveness of the blinding strategy using blinding indices. • Ensuring the administrative processes of randomisation and data management work well within the study. • Assess adherence to the conditions of the protocol. • Provide evidence to inform sample size calculation for a future study.

- **Schematic of Study Design**:


Screening & Enrollment
Patient requiring neck dissection identified in clinic
Screening for eligibility and trial information
Informed consent taken
Baseline recording of pain (VAS) and Neck Dissection Impairment index (NDII)
Randomised pre-operatively
Patient undergoes planned surgery
Allocation revealed at point of wound closure
Allocated to Fibrin Sealant
Allocation
Allocated to control
Post-operative Inpatient
Daily assessment of AEs (Clavien-Dindo)
Daily recording of pain VAS
Twice daily drain volume recording
Daily assessment of drain removal Daily
Assessment for hospital discharge
Follow-Up 1 (day 7 - 14)
Removal of clips/sutures
Assessment of AEs
Follow-Up 2 (day 28 - 42)
Assessment of AEs, NDII, WHQ, Pain VAS, blinding index, MCID
Analysis
Assessment of pilot study outcomes: missingdata, recruitment, randomisation, blinding, protocol adherence, follow-up

2 BACKGROUND INFORMATION

2.1 Introduction

The Problem Being Addressed

Complications after major surgery are a significant cause of morbidity and mortality and have been shown to have a negative impact on long-term quality of life and psychosocial well-being.1, 2 In surgical oncology, complications can also delay adjuvant treatment (e.g. radiotherapy) which is known to adversely affect survival.3 Neck dissection is one of the most commonly performed 'major operations' in head and neck surgical oncology and it is estimated, from national audit data, that approximately 7000 major head and neck surgical resections are performed each year in England alone.4 Significant surgical complications occur in approximately 10 – 20% of patients undergoing neck dissection.5, 6 Such risks increase to 40% in patients who have had previous chemo-radiotherapy to the area7 or when operating on higher risk patients of increasing age, with multiple co-morbidities and polypharmacy.8 Common surgical complications include: haematoma formation, surgical site infection, wound breakdown/dehiscence, and fistula formation. Management of these complications is frequently painful, invasive and may involve returning to theatre. This inevitably delays recovery, which in turn may result in prolonged hospital stay and immobility; both of which are known risk factors for lower respiratory tract infections and venous thromboembolism.

The Patient's Perspective

The direct impact on patients of complications following neck dissections has been borne out by recent and ongoing qualitative research. Currently unpublished doctoral research from colleagues at the University of Liverpool seeking a 'Core Outcome Set' for head and neck cancer has found that 'need for further surgery or invasive treatment' is considered 'very important' in >70% of patients through the Delphi method.9 This is reinforced by work done at the University of Bristol on a 'Core Information Set' for the broader topic of head and neck surgery that found 'likelihood of wound problems' and 'complications that may require a return to theatre' are both core elements of importance to patients in the consent process.10 Patients from the 'Aintree Head & Neck Cancer Patient Research Forum' have specifically highlighted their aversion to surgical drains finding them both painful and a significant barrier to mobilisation. Patient opinion is further supported

by robust data from a meta-analysis on the use of surgical drains in thyroid surgery that found they increased post-operative pain and infection rates.11 Clearly drains serve an important role in preventing potentially life threatening complications due to neck swelling, however reduction in the duration of their use, through early safe removal, and in reduction of wound-related complications will clearly translate to significant patient benefit in the immediate post-operative period.

Fibrin Sealants

A recent systematic review and meta-analysis on the use of Fibrin Sealants (FS) in head and neck surgery has found potential clinical advantages to both patients and healthcare organisations through reduction in complications and volume of wound drainage, thereby minimising the retention time of the drains.12

FS are commercially available, US Food and Drug Administration (FDA) approved, products that have been investigated broadly across several areas of surgery.13 FS is applied to the raw surfaces of the surgical wound prior to closure providing an adjunct to haemostasis. The mechanism of action is through replication of the final stages of the clotting cascade through which thrombin cleaves fibrinogen to form a fibrin clot. The subsequent clot effectively seals small vessels and occludes cavity dead space by adhering the wound surfaces, both essential steps in avoiding haematoma formation that may compromise surgical site healing. Results of previous investigations of FS effectiveness in surgery have been variable and have frequently been unduly influenced by poor study design.

The key relevant findings of this systematic review and meta-analysis were:

- There is a paucity of high-quality trials on the use of FS in Head and Neck surgery.
- There was a tendency for FS to reduce drainage volume (mean difference 26.86ml, 95%CI -43.41 to - 10.31, I2 =97%, p=0.001).
- There was a suggestion that FS may reduce 'mean retention time of drains' by 1.24 days (95%CI -3.32 to 0.85, I2 =99%, p=0.25) and 'hospital length of stay' by 2.09 days (95% CI -5.18 to 0.99, I2 =97%, p=0.18) but these were not statistically significant.
- Whilst not reaching statistical significance, FS may be protective against complications compared to standard of care with a relative risk of 0.69 (95% ci 0.35 to 1.38, I2 =0%, p=0.29). The benefit of FS was greater with regards to haematoma/seroma formation (RR 0.49, 95%CI 0.22 to 1.07, I2 =0%, p=0.07).
- Patients at high-risk of complications (e.g. anticoagulation and previous surgery or radiotherapy) were excluded from all studies analysed, leaving the effects of FS in populations most likely to benefit not assessed.
- The role of FS in lateral neck dissection is an area of need for further studies. Only 2 trials have been performed so far that have randomised 78 patients between them.14,

15 Their inclusion criteria and findings varied greatly and substantial statistical heterogeneity impaired conclusive results in the meta-analysis.

2.2 Rationale

With an understanding of the evidence in combination with clinical experience it is felt that a surgical trial to determine the effectiveness of FS in reducing the rate and severity of complications in patients undergoing lateral neck dissection is warranted. This important clinical question is framed by patient opinion and guided by a clinical desire to reduce morbidity, and indeed it has the potential to translate to patient benefit. However given the difficulties in the delivery of Head and Neck

surgical trials,16 this external pilot study will be used to answer critical questions on how well key components of the proposed study design work together as well as feasibility of the future trial.

2.3 Objectives

The key objectives of this randomised external pilot study are to assess the following points:

I. Whether patients can be recruited and retained at a rate of approximately 4 patients per month across the 2 centres.

II. Determining the effectiveness of the blinding strategy using blinding indices.

III. Ensuring the administrative processes of randomisation, allocation concealment and data management work well within the study.

IV. Assess adherence to the conditions of the protocol.

V. Provide evidence to inform the sample size calculation for the future phase III multicentre randomised trial

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Each of the following risks has been documented as either potential or theoretical in nature, their occurrence is expected to be highly unlikely should the trial protocol be adhered to. They are detailed in full below.

As Fibrin Sealants are derived from human blood they may contain infectious agents which can cause disease, such as viruses and theoretically, the agent that causes Creutzfeldt-Jakob Disease (CJD) in humans. The manufacturer states that certain measures have been taken to prevent infections. These include: selection of donors,

screening of individual donations for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, the possibility of transmitting infective agents cannot be totally excluded. The measures taken by the manufacturer are considered to be effective against viruses such as Human Immunodeficiency Virus (HIV), Hepatitis A, B and C. The measures taken may be ineffective against parvovirus B19. Parvovirus B19 infection may be serious for pregnant women as it may cause foetal infection. Pregnant women have therefore been excluded from taking part in this study. There have been no reports of transmission of infectious agents through the application of Fibrin Sealants in the literature. All patients will be informed of this potential risk during the consent process.

Administration of Fibrin Sealants may result in allergic reactions in some patients. The precise frequency of severe life-threatening reactions is unknown as they are incredibly rare. Patients who have a known allergy to Aprotinin (an ingredient of Fibrin Sealants that can cause allergic reactions) will be excluded from taking part in the study. The risk of Aprotinin hypersensitivity is increased in patients who have been exposed to it within 6 months or are allergic to bovine proteins (as the synthetic Aprotinin used in Fibrin Sealant is structurally identical to bovine Aprotinin). Therefore patients who have been exposed to Fibrin Sealant within 6 months prior to recruitment or are allergic to bovine proteins (e.g. dairy products), will be excluded from the study.

Because the Fibrin Sealant is applied to the wound as a spray driven by ‘medical grade air’, it is possible that the patient may develop an ‘air embolism’. There have been 6 reported cases of air embolism following the administration of Fibrin Sealant. It is thought that these cases occurred because either the air pressure was too high or the spray device was held too close to the wound. The manufacturer recommends that the air pressure should be no higher than 1.7 bars and the spray device should be held no closer than 10 centimetres to the wound. These recommendations have been incorporated into the study protocol. Every surgeon that uses Fibrin Sealant on a patient in this study will undergo training by the research team. They will need to demonstrate their understanding of these recommendations by setting up the spray device and entering the correct settings into the machine. They will also need to demonstrate their spraying technique where the distance from the wound will be assessed. Only when they can demonstrate safe use of the Fibrin Sealant will they be accredited to use it on study participants.

Other more minor risks of using Fibrin Sealants include itchiness of the skin (occurs in 2/138 patients), a collection of fluid under the skin (occurs in 1/138 patients) and problems with skin grafts (5/138 patients). The latter risk is not relevant to this study as we will not be using the Fibrin Sealant on skin grafts. Problems with itchiness and fluid under the skin will reported as adverse events/complications and treated on a case-by- case basis.

2.4.2 Known Potential Benefits

There are no known patient benefits however, every effort has been made to minimise inconvenience to study participants by making the research pathway as similar to the normal clinical pathway as possible. As a result the patient has the opportunity to participate in research without a significant burden of extra tests or hospital visits.

3 SELECTION OF CENTRES/CLINICIANS

Each participating centre will be required to offer the following minimum requirements:

1) Centres will either have or be part of a comprehensive Head & Neck Multidisciplinary Team (MDT).

2) Have surgical expertise in the management of Head & Neck Cancer.

3) Have sufficient caseload to recruit 2 patients per month.

4) Demonstrate enthusiasm to participate in the study.

5) Provide information to all supporting staff members involved with the trial or with other aspects of the patient's management.

6) Acknowledge and agree to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to Good Clinical Practice (GCP).

3.1 Centre/Clinician Inclusion Criteria

1) Positive Site Specific Assessment (SSA) by the centre's Research & Development (R&D) Department.

2) Completed Research Site Agreement.

3) Receipt of evidence of completion of points 1) and 2) by NWSTC.

4) Completion and return of 'Signature & Delegation Log' to NWSTC.

5) Personnel on delegation log have attended the proposed site initiation and training days and have been accredited to perform the intervention.

6) Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI).

7) CV including ICH GCP training – other personnel on the delegation log.

8) Clinical Study Protocol Receipt Form.

9) Patient Information Sheets (PIS) and Informed Consent Form (ICF) on trust letter headed paper.

10) Completion of test SAE reported via web.

3.2 Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

4 TRIAL DESIGN

4.1 Overall Design

Determining the effectiveness of fibrin sealants in reducing complications in patients undergoing lateral neck dissection: a randomised external pilot trial (Acronym: DEFeND). The study design that is being piloted is that of a parallel group superiority trial with patients being randomised in a 1:1 ratio to each arm. The interventional arm will constitute the application of ARTISS (Baxter Healthcare LTD) fibrin sealant to the surgical wound in addition to “standard of care”. The control arm will constitute “standard of care” alone (described in more detail in section 7). Both patients and outcome assessors will be blinded to the allocation. An approximate sample size justification of 50 patients (25 in each arm) has been chosen, as this will provide sufficient precision to calculate the sample size required for the future phase III trial. Currently the design of the pilot study mirrors the design of the future phase III trial, however it is expected that refinements will be necessary based on the pilot data. Patients will be stratified according to the hospital they receive their treatment.

4.2 Pilot Study Outcomes

The proposed outcome measures for this study can be divided into those that are specific to the pilot study and those that would potentially inform a future trial to determine the effectiveness of fibrin sealant in neck dissection. As this is a pilot study, no formal assessment of efficacy, cost or safety across treatment arms are made. All analysis shall take the form of summary statistics and graphical summaries. Continuous data shall be presented using medians (inter-quartile ranges) and categorical data shall be presented as frequencies of counts with associated percentages.

The outcomes for the pilot study include:

- Proportion of eligible patients recruited to the study, calculated as the screened:randomisation ratio.

- Reasons for failure to screen potentially eligible patients.
- Recruitment rate measured as the number of patients randomised each month.
- Reasons for failure to randomise.
- Reasons for failure to reveal allocation at a specific time point during surgery.
- Fidelity of the blinding process (both patients and outcome assessors) as detected by blinding indices.
- Accuracy of data recording, summarised by the number of key data items with missing/incomplete data entries.
- Number of patients lost to follow-up.
- Protocol adherence, measured by the number of major/minor protocol deviations observed through the study.
- Determining the minimal clinically important difference (MCID) in clinical endpoints by questioning recruited patients and recruiting clinicians.

4.3 Clinical Endpoints of Future Phase III Trial

Any surgeon who is in theatre after the revealing of allocation is unblinded and must delegate post-operative clinical decisions and reporting of clinical endpoints to an appropriate colleague who is blinded.

- Clavien-Dindo classification of surgical complications (**Appendix A**).
- Twice daily wound drainage volume (ml).
- Assessment of time to drain removal in hours from departure from theatre.

- Assessment of time to being declared ‘medically fit for discharge’ and actual hospital

discharge in hours from the time of 'end of surgery'.

Patient reported outcomes to be assessed for use in the future phase III study are:

- Neck Dissection Impairment Index (NDII). This is a procedure specific patient reported outcome measure (**Appendix B**).
- Daily patient reported pain score using Visual Analogue Scale (VAS) (**Appendix C**).
- Wound Healing Questionnaire (WHQ). This is a questionnaire currently in the process of validation to assess wound healing after surgery (Appendix D).

5 STUDY POPULATION

The pilot study setting will be Aintree University Hospital and Queen Victoria Hospital. These are both specialist hospitals for the management of Head & Neck Cancer in the UK.

5.1 Inclusion Criteria

- Patients due to undergo lateral neck dissection
- Neck dissection to include a minimum of 3 levels
- Patients who have capacity to consent

5.2 Exclusion Criteria

- Age < 18 years
- Bilateral neck dissection
- Presence of a vascular pedicle for reconstruction
- Pregnancy or breast feeding
- Known hypersensitivity reaction to Aprotinin
- Previous exposure to Fibrin Sealant within 6 months
- Known allergy to dairy products

5.3 Patient Transfer and Withdrawal

By completing the DEFeND consent process, patients are consenting to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

5.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP. A copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The NWSTC should be notified in writing of patient transfers.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

1) At their request or at the request of a legal representative.

2) A change in surgical plan after enrolment such that the patient no longer meets the eligibility criteria.

3) The investigators deems further involvement in the study detrimental to the wellbeing of the patient

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow- up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly withdraws consent for follow-up (see section 5.3.3).

5.3.3 Withdrawal from Trial Completely

Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS

mechanisms. If the patient explicitly states their wish not to contribute further data to the study, a withdrawal CRF should be completed.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

Patients eligible for the DEFeND trial will be screened through outpatient clinics and/or Head & Neck MDT. The steps that will be completed on all patients to ensure they meet enrolment criteria include:

- Clinical examination
- Detailed medical history including previous treatment/surgery to the head & neck
- Clinical decision to offer a lateral neck dissection

A pre-screening log of all potential patients should be kept at each site, including individuals who decide not to participate in or are found to be unsuitable for the study.

Screening will be performed upon a patient's possible eligibility for the study as above and must be documented on the NWSTC Web Portal "Screening and Enrolment log". Screening details should be entered into the portal and this will automatically generate a screening number and a confirmation email with these details will be sent to site staff. The screening log can be printed at any time off the Portal to allow for storage in the Investigator Site File.

Step-by-step guides will be issued to research site staff and the process will also be demonstrated during site initiations. All patients will be issued a screening number and, where possible, for patients who are not randomised a reason is recorded. The importance of this is in establishing the screening:randomisation ratio which is a key endpoint of the pilot trial.

6.2 Enrolment/ Baseline

Once the criteria for successful screening are complete, and at that point indicate a patient likely to meet eligibility criteria, the patient may be given information about the trial by means of careful explanation with the help of a PowerPoint presentation, Patient Information Sheets and introduction to the Research Practitioner.

The patient will be told that their lack of participation will not impact on the quality of their care. If they wish to consent they will be told that they may change their mind at any time. After signing the consent form, any necessary additional investigations are carried out prior to randomisation:

- Demographics (height, weight, age, gender, smoking and alcohol status).
- Pre-operative neck pain Visual Analogue Scale (VAS) and Neck Dissection Impairment Index (NDII) questionnaire (**see Appendix B and C**).
- Blood tests including full blood count, clotting screen (INR and APTT), liver function tests
- A pregnancy test (beta-hCG blood test) for women of childbearing age will be offered.

If offered, the pregnancy test needs to be carried out prior to randomisation as it constitutes an eligibility criteria. The other information mentioned above should also be carried out before randomisation as it constitutes important baseline measurements.

Patients will be enrolled onto the study by NWSTC once the following documents have been forwarded by the local investigator or research nurse:

1. Eligibility checklist
2. Enrolment forms
3. Copy of signed Patient Consent Form

When the patient has been enrolled a confirmation email will be sent to the site detailing the patients MACRO ID, site, patient initials, DOB, screening number, proposed date

of surgery, details of consent and a link to the patient in the Treatment Allocation Randomisation System (TARDIS). The investigator will also be sent a link to a bespoke web based application for the DEFeND study. This bespoke application should only be accessed during surgery at the point of wound closure.

6.3 Randomisation

The process of randomisation will be undertaken pre-operatively using the TARDIS software. The allocation will be concealed to everyone including the person performing the randmisation. Once the patient has undergone their neck dissection and immediately prior to the point of wound closure, the theatre team will login to a bespoke wed based application. Once logged in to this application the surgical team will enter data regarding the surgery including start time and surgeons present in theatre. Once this data has been entered the allocation will be revealed. This allocation will be revealed for a period of 30 minutes before being concealed once more.

As part of the blinding strategy, any clinicians who will be assessing study outcomes must leave theatre prior to the revealing of treatment allocation. They must not return until the theatre has been cleared of any evidence of ARTISS usage. The surgeon administering the ARTISS will not be allowed to assess study outcomes for the patient and must delegate this responsibility to a suitable colleague.

To randomise, the research nurse will need to create a patient file on the MACRO database and enter the baseline parameters. Following this the research nurse should follow the link to TARDIS in the enrolment confirmation email. The research nurse will be prompted to confirm eligibility of the patient along with the stratification factor, this will enable randomisation to one of the two treatment arms. As stated before, although the patient has been randomised, their allocation will be concealed. The allocation will be revealed for a 30 minute window in theatre.

Patients will be randomised to either ‘ARTISS’ or ‘Standard of Care’ in a ratio of 1:1. Randomisation lists shall be produced by a statistician at the NWSTC prior to the recruitment of the first patient. Lists shall be produced based on the principle of

randomly permuted blocks with random block sizes of 2 and 4. Patients will only be stratified according to the hospital in which they receive their treatment.

Randomisation 24 hours a day (including public holidays) via web

7 TRIAL TREATMENT/S

7.1 Introduction

Patients will be randomised in a 1:1 ratio between arm A and arm B. Arm A constitutes ARTISS (Baxter Healthcare LTD) in addition to “standard of care”. Arm B constitutes “standard of care” only.

7.2 Arm A: Neck dissection with fibrin sealant and standard wound closure

Interventional Arm: Application of ARTISS fibrin sealant to the surgical wound in addition to “Standard of care”. “Standard of care” will include the establishment of a dry surgical field after performing the neck dissection using electrocautery &/or surgical ties &/or clips. The wound should then be irrigated with 100ml of Normal Saline and dried. Up to 2ml of ARTISS will be sprayed into the wound adhering to the manufacturer’s instructions and surgical protocol steps as defined below.

7.2.1 Formulation, Packaging, Labelling, Storage and Stability

ARTISS is a Fibrin Sealant (FS) manufactured by Baxter Healthcare LTD. Further details regarding this product can be found in the manufacturer’s ‘product information

sheet’ in **Appendix E**. For the purposes of this study we will be using the 2ml pre-filled

double chamber syringe preparation. ARTISS is licenced for use in the hospital setting and by surgeons trained in its application. Baxter Healthcare LTD describes the therapeutic indications of ARTISS as “a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples. In addition, ARTISS is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces.” Baxter Healthcare LTD describes the **contraindications** of ARTISS as:

a) Treatment of massive and brisk arterial and venous bleeding

b) Intravascular application

c) Hypersensitivity to the active substances or to any of the excipients

ARTISS has a shelf life of 2 years and should be stored and transported in a frozen state at < -20oC. The syringe must be kept in the outer container in order to protect from light. Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25oC). It is important not refreeze or refrigerate after thawing.

7.2.2 Preparation, Dosage and Administration of Study Treatment/s

Preparation

The inner bag and its contents are sterile unless the integrity of the outside package is compromised. It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum- coated plastic bags). The protective syringe cap should not be removed until thawing is complete and the joining piece is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

There are several methods of thawing the ARTISS, some of which take over 1 hour. Given that the patient's allocation will be revealed intra-operatively at the time point immediately prior to wound closure, this study will utilise the "Quick Thawing" technique. Quick thawing is done by removing the ARTISS from the aluminium-coated

plastic bags and placing it in a sterile water bath at 33°C to a maximum of 37°C. It is recommended to use an infrared thermometer to check the water temperature prior to placing the ARTISS syringe in the water bath. The prefilled syringe is kept in the water bath for 5 minutes ensuring the contents are completely immersed. It is important to note that ARTISS cannot be thawed in your hands or in a microwave. After 'Quick Thawing' ARTISS may be stored at 33 – 37°C for a maximum of 4 hours. A flow chart summarizing the "Quick Thaw" technique can be found in **Appendix F**.

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration or any variation in physical appearance. In the event of either being observed, the solution should be discarded. The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have denatured (e.g. due to an interruption of the cold storage chain or by overheating during warming). In this case, ARTISS must not be used.

The next stage is to set up the EASYSPRAY pressure regulator device. Ensure there is a charged 9V battery and connect it to an IV pole or trolley using the clamps on the back of the device. Use a suitable connection tube to connect the EASYSPRAY device to medical air. Set the spray pressure to 1.5 bar.

Firmly attach the spray head to the nozzle of the double-chamber syringe containing the thawed ARTISS. Fasten the 'pull strap' to the double-chamber syringe to assure the spray head is tightly secured. Fit the EASYSPRAY connection tube to the luer-lock connector on the underside of the spray head. Attach the clip on the end of the sensor line to the syringe plunger (pressing this clip emits air through the spray set). The ARTISS is now ready for use. A copy of the quick reference guide for setting up the EASYSPRAY pressure regulator device published by Baxter Healthcare LTD can be found in **Appendix G**.

Administration

The administration of ARTISS requires at least 3 people including a scrub practitioner, assistant and surgeon. While the ARTISS is being thawed the surgeon should irrigate the wound with 100ml of Normal Saline, dry the wound with gauze swabs, secure the surgical drain and place several resorbable parachute sutures across the platysma layer. These sutures should be loosely clipped and not tied to ensure good access to the wound. The drain should be held temporarily outside of the wound to ensure the perforations are not occluded by the ARTISS. The prepared spray set should not be held any closer than 10 cm to the wound to avoid the risk of air embolism. Once the application of ARTISS has commenced the surgeon has 60 seconds to administer up to 2ml and manipulate the skin flaps into position prior to polymerisation. It is therefore important to strictly adhere to the time using a stopwatch during the application of ARTISS. The assistant should retract any structures (e.g. sternocleidomastoid muscle) to ensure the surgeon can reach these sheltered areas and apply the ARTISS evenly in a thin layer across the entirety of the wound. It is not absolutely necessary to use the full 2ml, it is more important to apply the ARTISS in a thin layer avoiding pooling and large droplet formation. Once the ARTISS has been applied the drain and skin flaps repositioned and even pressure applied to the wound (using a large rolled up gauze swab) while the surgeon ties off all of the parachute sutures. It is very important that the surgeon does not lift the skin edges up while tying the sutures as this may break any adhesive bond created by the sealant. The surgical vacuum drain should then be activated and the assistant should maintain pressure on the neck for a full 3 minutes. After 3 minutes clips/staples are used to close the skin edges. When spraying the ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO2 should be monitored because of the possibility of air embolism. A flow chart summarising this surgical protocol can be found in **Appendix H**.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7.2.3 Dose Modifications

A maximum of 2ml of ARTISS can be applied. It is at the surgeon's discretion how much of the 2ml is applied. It is important that the ARTISS is applied in an even and thin layer avoiding pooling and droplet formation.

7.2.4 Accountability Procedures for Study Treatment/s

Baxter Healthcare LTD has agreed to support the study in terms of ensuring adequate supplies of ARTISS and the associated equipment. If there any faults with the equipment Baxter Healthcare LTD will either repair or replace the equipment in keeping with their standard customer service procedures.

7.2.5 Assessment of Compliance with Study Treatment/s

Only surgeons who have received training and have been accredited will be permitted to use ARTISS within this trial. NWSTC will cross-reference the names of the surgeons on the operation note with the delegation log. Compliance will be granted if at least one member of the operating team present during the administration of ARTISS has received training.

7.3 Arm B: Neck dissection with standard wound closure

Arm B is the control arm and constitutes "standard of care" alone. This will include the establishment of a dry surgical field after performing the neck dissection using electrocautery &/or surgical ties &/or clips. Patients will have a surgical drain placed and the wound closed in the usual manner.

7.4 Unblinding

It is unlikely that this trial will require unblinding as the ARTISS is administered only once in the theatre environment. The surgeon applying the ARTISS will not be blinded. The patient, surgeons assessing outcomes, ward nurses and research nurses will be blinded. The main clinical endpoints of interest (Clavien-Dindo, removal of drain, fitness for discharge) require the assessment of a surgeon. Therefore operating surgeons (who are unblinded) need to delegate these assessments to suitable blinded colleagues. Details of potential risks/complications associated with ARTISS are provided in section 2.4.1.

A severe hypersensitivity reaction, air embolism or transmission of an infective agent constitute a serious adverse event. If they occur, severe hypersensitivity and air embolism would be anticipated to occur during or immediately after administration in the theatre setting. Staff caring for the patient at this time will not be blinded so there will not be a delay in diagnosis and emergency management. Fortunately these adverse events are incredibly rare, however if they did happened, the patient, outcome assessors and nursing staff would be unblinded only if the information is required for the ongoing medical management of the condition.

In the event that the patient is diagnosed with an infectious disease that was not diagnosed pre-operatively, they will be unblinded. Based on the 'Serious Hazards of Transfusion' 2016 annual report, the following infectious diseases are known to have been transmitted via blood products in the UK:

1. Hepatitis A, B, C or E
2. Human Immunodeficiency Virus (HIV)
3. Parvovirus (B19)
4. Cytomegalovirus (CMV)

5. Human T-cell Lymphotropic Virus (HTLV) types I and II
6. Malaria
7. Variant Creutzfeldt-Jakob Disease (vCJD) or any other prion disease

If the patient is newly diagnosed with any of the above infectious diseases, they will be unblinded and immediately referred to the appropriate medical specialists for treatment.

7.5 Concomitant Medications/Treatments

There are no restrictions on concomitant medications/treatments.

- **7.5.1 Data on Concomitant Medication**

Only data on concomitant anticoagulant and anti-platelet medication will be collected.

7.6 Overdoses

No case of overdose has been reported.

7.7 Co-enrolment Guidelines

Patients who are currently participating in another clinical trial of an investigational medicinal product (CTIMP) will not be recruited to this study.

Patients who meet the eligibility criteria and are participating in a subsequent study which is not a CTIMP, may be approached and recruited provided there are no consequences to the scientific validity of either study. Co-enrolment remains at the discretion of the Principal/Chief Investigators for the respective trials.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule of Trial Procedures

Participants will be involved in the study for 6 weeks from the date of surgery. Post- operative assessments, including daily in-patient and follow-up visits, must be conducted by a blinded member of the trial team. The randomising surgeon MUST NOT conduct any of the post-operative assessments.

						Follow-Up Schedule				
Procedures										
Identify potential participant	X	X								
Approach potential participant to discuss study	X	X								

Medical history			X								
Physical examination			X								
Assessment of eligibility criteria			X								
Review of concomitant anticoagulant medications			X	X	X	X	X	X	X	X	X
Review of previous treatment to ipsilateral neck			X								
Demographic assessment			X								
Signed consent form					X						
Randomisation					X						
Assessment of patient reported outcome measures	Neck pain (VAS)				X		X	X	X	X	X
	Neck Dissection Impairment Index (NDII)				X					X	X
	Wound Healing Questionnaire (WHQ)									X	X
Surgical Protocol	Neck dissection surgery					X					
	Allocation revealed at point of wound closure					X					

	Prepare and administer ARTISS (interventional arm only)					X					
Assessment of Clinical Outcome Measures	Assessment of AEs (Clavien-Dindo)					X	X	X	X	X	X
	Twice Daily Wound Drainage Volume (ml)						X				
	Wound Drain Removal						X				
	Hospital Discharge						X				
Assessment of Pilot Study Outcomes	Assessment of Blinding Strategy									X	X
	Assessment of Minimal Clinically Important Difference									X	X

							Follow-Up Schedule				
Procedures											
Laboratory Tests	Full Blood Count**				X						
	INR & APTT				X						
	Pregnancy test (women of childbear-ing age)				X						
	Microbiology Swab from Neck Wound & Oral Cavity					X	X	X	X	X	
	Histological Lymph Node Yield									X	

Figure 1. Schedule of DEFeND enrolment, interventions and assessments (SPIRIT)

(X) – As indicated/appropriate.

*At baseline, all procedures should be done before study intervention.

**Full Blood Count must include Hb concentration, platelet count and white cell count

8.2 Procedures for assessing Efficacy

A central review process will be undertaken to assess the neck dissection specimen which should include 3 or more levels of the neck. Lymph node yield will be used as a proxy to assess the extent of surgery.

8.3 Procedures for Assessing Safety

Safety will be assessed through reporting on post-operative complications as described in section 10 and **Appendix A**. All post-operative complications that occur from the time of surgery up to data collection at week 6 will be reported.

8.4 Other Assessments

8.4.1 Quality of Life and Health Economics

Neck Dissection Impairment Index (NDII)

The NDII is a procedure specific Health Related Quality of Life (HRQoL) assessment tool. The tool is validated for use in patients who have undergone selective or modified radical neck dissection.18 Although the NDII is not validated for use 6 weeks after surgery, there is evidence that the NDII score at this early juncture is representative of longer-term HRQoL.19 A copy of the NDII questionnaire can be found in **Appendix B.**

Incremental Cost-Effectiveness Ratio (ICER)

The health economic (HE) assessment of using fibrin sealant (ARTISS) will be piloted using the 'incremental cost-effectiveness ratio' (ICER). This will calculate the average incremental cost associated with each surgical complication prevented when compared to 'standard of care' (SOC) treatment without ARTISS. This will be calculated using the following equation:

$$\text{ICER} = \frac{\text{Overall cost of ARTISS arm} - \text{Overall cost of SOC arm}}{\text{No. of complications in ARTISS arm} - \text{No. of complications in SOC arm}}$$

The variation in costs between the treatment arms will be calculated individually for each patient based on their time in the operating theatre (including returns to theatre), their length of stay within each ward type, their number of hospital visits in the immediate post-operative period (both planned and unplanned), and the cost of materials (including those required to administer ARTISS).

8.4.2 Special Assays or Procedures

Microbiology swabs will be taken for the sub-study (see section 8.5). This will include taking a standard hospital microbiology swab from the neck wound and oral cavity. These samples will be taken intra-operatively by the surgeon and by nursing staff on the ward and outpatient department. A member of the Institute of Infection & Global Health, University of Liverpool, will collect these samples.

8.5 Sub-studies

Development of novel biomimetic antimicrobial therapies to mitigate against bacterial wound infections following Head & Neck Cancer surgery.

A promising strategy for the next generation of antimicrobial therapeutics will be to specifically target the bacteria's signalling pathways inhibiting biofilm formation and detachment. Theoretically, by disrupting bacterial signalling pathways, there should be a lower tendency for the bacteria to develop defence responses and resistant mutants. The gene-expression

patterns of biofilms differ from planktonic bacteria and deciphering the genetic basis of biofilm formation will allow for an inherent understanding of the formation of these sessile communities and their inherent resistance to antimicrobial agents. Biofilms develop an ordered structure whereby bacteria are embedded in a protective exopolysaccharide matrix. This, along with other factors, can make bacterial biofilms incredibly resistant to treatment. In addition, bacteria within biofilms can form multispecies communities which can further complicate treatment regimens with consequent negative clinical outcomes.

Using clinical samples from infected and non-infected neck wounds, molecular characterisation of microbial communities through sequencing will allow the identification of the different bacterial species within the wounds and through network analysis, identify associations with the risk of poor clinical outcomes and prolonged treatment. Furthermore, as part of this work a model of biofilm dispersal will be developed to understand the risk of infection dissemination and enable testing of the novel therapeutics under infection–relevant conditions. This will provide the underpinning knowledge to rationally design efficacious antimicrobial therapeutics that do not lead to antimicrobial resistance.

This aim will be realised though the following objectives:

- Isolation of and 16S rRNA microbiome sequencing of clinical samples from infected and uninfected head and neck surgery patients.
- Encapsulation of naturally derived antimicrobials in currently utilised, aerosol-applied, fibrin sealants for controlled and sustained release.
- Testing of efficacy of antimicrobial/fibrin capsules on clinical isolates.
- Benchmarking of efficacy of antimicrobial therapeutics on laboratory reference strains vs. clinical isolates.
- Develop biofilm dispersal model.

This sub-study will not impact on the main study. Patients who develop neck infections within this study will require microbiology samples as part of their standard care. The only additional samples required for this sub-study will be non-invasive samples from the neck wound and oral cavity in the form of standard hospital microbiology swabs.

8.6 Loss to Follow-up

If any of the trial participants are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the participant's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information they may have to the recruiting centre.

All patients, whether lost to follow up or not, will have their data collected at week 6.

8.7 Trial Closure

Investigators will be informed when patient recruitment is to cease.

Trial enrolment may be stopped at a site when the total number of participants for the trial has been obtained.

The trial will close once all the subjects that have been randomised have completed six weeks of post-surgical follow up, all centres have completed and returned all necessary (e)CRF's.

The TSC may stop the trial prematurely. Such premature termination / suspension of the trial will be notified to the MREC as required.

The trial will be considered formally closed when the database is locked.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

This section contains an overview of all statistical considerations for the DEFeND trial including details on trial design patient randomisation and an overview of the statistical methodology used. Note that a separate Statistical Analysis Plan (SAP) will be produced to give full details of all data analysis in the study.

9.2 Method of Randomisation

Randomisation lists shall be produced by a statistician at the NWSTC prior to the recruitment of the first patient. Patients shall be randomised using a 1:1 ratio. Lists shall be produced based on the principle of randomly permuted blocks with random block sizes of 2 and 4. Patients will only be stratified according to the hospital in which they receive their treatment.

9.3 Outcome Measures

As DEFeND is an external pilot study, trial outcomes are categorised into those which address deliverability and feasibility of a larger study, those which address clinical outcomes of patients in the study and patient reported outcomes which will inform patient perspectives of the study and its interventions.

9.3.1 Pilot Study Outcomes

- Proportion of eligible patients recruited to the study, calculated as the screened to
- randomisation rate.
- Reasons for failure to screen potentially eligible patients.

- Recruitment rate measured as the number of patients randomised each month.
- Reasons for failure to randomise.
- Reasons for failure to reveal allocation at a specific time point during surgery.
- Fidelity of the blinding process (both patients and outcome assessors) as detected by blinding indices.
- Accuracy of data recording, summarised by the number of key data items with missing/incomplete data entries.
- Number of patients lost to follow-up.
- Protocol adherence, measured by the number of major/minor protocol deviations observed through the study.
- Determining the minimal clinically important difference (MCID) in clinical endpoints by questioning recruited patients and recruiting clinicians.

9.3.2 Clinical Endpoints of Future Phase III Trial

- Clavien-Dindo classification of surgical complications (**Appendix A**)
- Daily wound drainage volume (ml)
- Time (hours) for daily wound drainage volume to reach <30ml/24hrs
- Time (hours) to drain removal (as dictated by drainage volume)
- Total wound drainage volume (ml)
- Time (hours) to be declared medically fit for hospital discharge and time (hours) to actual hospital discharge
- Incremental cost-effectiveness ratio

9.3.3 Patient Reported Outcomes

- Neck Dissection Impairment Index (NDII). This is a procedure specific validated patient reported outcome measure (**Appendix B**)

- Daily patient reported pain score using Visual Analogue Scale (VAS) (**Appendix C**)
- Wound Healing Questionnaire (WHQ). This is a questionnaire currently in the process of validation to assess wound healing after surgery (**Appendix D**).

9.4 Sample Size

As this is a pilot study, no formal power/sample size calculation based on clinical data is given. For this study the two main outcomes of interest are to determine accurate estimates of the rate of recruitment (being the number of patients recruited relative to the number eligible) and to collect sufficient clinical data to accurately estimate a sample size for a future study. It is estimated that over the study period, approximately 50 patients will be recruited at rate of 30%. Based on this, 50 patients (25 in each arm) will produce a standard error of approximately 6.5% and a 95% confidence interval of approximately (17 – 43%) will be obtained. With respect to surgical complication rate, being the clinical outcome of current greatest interest, even if a response rate of 50% is observed then a 95% confidence interval of (0.36, 0.64) will be observed which provides sufficient precision for a future sample size.

9.5 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at 6 monthly intervals after the recruitment of the first patient. A formal Independent Data Monitoring and Safety Committee (ISDMC) will not be convened. In keeping with the guidance outlined in the document 'Guideline in Data Monitoring Committees' published by the Committee for Medicinal Products for Human Use, it is thought that an IDSMC is not required. This is because patients will be treated for a very short period of time (single administration during surgery) and Fibrin Sealants are well characterised and already widely used within healthcare. Although there are potential risks to patients, these are incredibly rare and known.

The independent members of the TSC (Chairperson, expert, statistician) will take responsibility for reviewing all interim safety data. The independent members will be asked to give advice on whether the accumulated data from the trial, together

with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. Given this is a pilot/feasibility study, it is anticipated that the TSC will only recommend termination on grounds of safety.

9.6 Statistical Analysis

9.6.1 Patient Groups

The primary analysis will be carried out on the full analysis set which will be depend on the intention to treat principle retaining patients in their initially randomised groups irrespective of any protocol violations

9.6.2 Missing Data

Missing data are expected to be small and final analyses are planned to be carried out on a complete case basis. If substantial missing data (>10%) are observed in either a study outcome or key prognostic covariate then multiple imputation using chained equations will be applied.

9.6.3 Levels of Significance

There are no formal comparison of treatment groups and therefore no levels of significance against which hypotheses should be tests. As a guide however, all reported results will be reported using nominal 95% confidence intervals.

9.6.4 Analysis of study outcomes

As this is an external pilot study, all data analyses shall take the form of descriptive statistics. Continuous data shall be summarised as medians with associated inter- quartile ranges and categorical data shall be summarised as frequencies of counts and associated percentages.

In terms of clinical outcomes, aside from descriptive statistics then informal comparisons between allocated groups will be made using difference in means for continuous covariates and difference in rated for categorical covariates.

9.6.5 Analysis of study toxicity

Adverse events (AEs) and serious adverse events (SAEs) shall be defined using CTC (Version 4) definitions. All AEs and SAEs shall be compared across groups using the TAME guidelines. Furthermore, the worst AE/SAE for each type for each patients shall also be retained and compared across treatment groups using a stratified Chi-Square test.

10 SAFETY

10.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6

Adverse Event (AE)

Any untoward medical occurrence (i.e. any unfavourable or unintended sign, symptom or disease) in a research participant to whom a surgical/clinical intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. **Surgical complications and adverse reactions to ARTISS fibrin sealant will be the only events reported to assess safety**.

Surgical Complication

Any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure (disease or condition that remains unchanged after surgery).20

Unexpected Adverse Reaction (UAR)

An adverse reaction the nature and severity of which is not consistent with the information about ARTISS set out in the summary of product characteristics. All UARs will be reported.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or adverse reaction is classified as serious if it:

1) results in death

2) is life-threatening* (subject at immediate risk of death)

3) requires in-patient hospitalisation or prolongation of existing hospitalisation**

4) results in persistent or significant disability or incapacity, or

5) consists of a congenital anomaly or birth defect

6) Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. **Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien Dindo grade IV or above (see **Appendix A**).

- An exacerbation of a pre-existing illness/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.

- An increase in frequency or intensity of a pre-existing episodic event/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.

- A condition (even though it may have been present prior to the start of the trial) detected after the trial surgery and/or use of ARTISS fibrin sealant.

- Continuous persistent disease or symptoms present at baseline that worsens following the trial surgery and/or use of ARTISS fibrin sealant.

10.2.2 Do Not Include

- Events including signs, symptoms and disease that are not deemed a complication of the trial surgery as per the definition above.
- Generalised signs and symptoms of having undergone major head and neck surgery

e.g. lethargy, difficulty with speech and/or swallow.

- Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien Dindo grade IIIb or below (see **Appendix A**).
- Extended hospital stay due to a delay in planned surgery.
- In-patient hospitalisation or prolongation of existing hospitalisation due to post- operative complications that are grade IIIb or below (see **Appendix A**).
- Medical or surgical procedures - the condition which leads to the procedure is the SAE.
- Pre-existing disease or conditions present before surgery that do not worsen.
- An exacerbation of a pre-existing illness/condition that is not deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- An increase in frequency or intensity of a pre-existing episodic event/condition that is not deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery.
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.

- Injury or accidents.
- Abnormal laboratory results.

10.2.3 Reporting of Pregnancy

Pregnancy is listed as an exclusion criterion for entry to the DEFeND trial.

In the event of a patient becoming pregnant after recruitment to the trial, this fact **should be reported as soon as possible to the C.I through NWSTC** (as if an SAE). The guiding principles in this event are:-

1) If the patient has not yet received treatment, or completed treatment, the patient may be withdrawn from the trial.
2) Once treatment is complete, i.e. the patient is in follow-up phase, it may well be possible to retain the patient to the conclusion of the trial.
3) A decision will be made in the best interests of the patient between the treating clinician and the C.I. as to retention in the trial and any continuing cancer therapy.

10.3 Notes Severity / Grading of Adverse Events (Surgical Complications)

The assignment of the severity/grading should be made by a blinded surgeon who has been delegated this responsibility by the operating surgeon. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the Clavien-Dindo Classification of Surgical Complications as detailed in **Tables 1 and 2** in **Appendix A**.20 **Table 1** describes the original Clavien-Dindo classification whereas **Table 2** provides an interpretation of the Clavien-Dindo classification for some common/established complications after Head & Neck Surgery relevant to this trial.

10.4 Relationship to Trial Treatment

The assignment of causality should be made by a blinded surgeon who has been delegated this responsibility by the operating surgeon using the definitions in Table 3.

Causality should be assigned to the following:

1. Anaesthetic
2. Generality of surgery (including surgical airway, primary tumour resection)
3. Neck dissection surgery
4. Use of ARTISS fibrin sealant

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the Research Ethics Committee (REC) will be informed of both points of view.

Table 3: Definitions of Causality

Relationship	**Description**
None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial

	intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

Expectedness will be assessed against the following:

1. Neck dissection surgery
2. Use of ARTISS fibrin sealant

Post-operative complications related to either neck dissection or use of ARTISS fibrin sealant that are Clavien-Dindo grade IIIb or below are **expected** for the DEFeND trial.

Post-operative complications related to either neck dissection or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above are **unexpected** for the DEFeND trial.

An AE (surgical complication) where the causal relationship to the study procedure (neck dissection and/or use of ARTISS fibrin sealant) is assessed by the investigator as “possible”, “probable”, “highly probable”, is graded as serious and unexpected (SUSAR) is subject to expedited reporting to the Research Ethics Committee (REC). This is the responsibility of NWSTC.

10.6 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

- **Appendix E: ARTISS Summary Product Information Sheet (section 4.8)**

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

All adverse events should be reported from the point of consent until 6 weeks after surgery. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the NWSTC in the first instance.

10.7.1 Non serious ARs/AEs

All non-serious expected and unexpected complications of surgery should be reported from the day of surgery at each post-operative study visit and throughout the follow up phase. All complications should be reported on the appropriate CRF and graded using the Clavien-Dindo Classification of Surgical Complications.

10.7.2 Serious ARs/AEs/SUSARs

All complications related to the neck dissection surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above must be reported as SARs, SAEs and SUSARs. They should be reported within 24 hours of the local site becoming aware of the event up to 6 weeks post-surgery. SARs, SAEs and SUSARs may be reported past 6 weeks if deemed appropriate to do so by the local investigator (e.g. the complication is considered to be related to the trial surgery).

The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the complication has not resolved at the time of reporting.

All complications related to the neck dissection surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IIIb or below that meet the definition of serious are exempt from SAE reporting. Such events should only be reported in the relevant section of the CRF.

Clarification on the Clavien-Dindo grading of common/established complications following major head and neck surgery is provided in Table 2 within Appendix A.

The NWSTC will notify the main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.

10.9 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the NWSTC on an SAE form unless the SAE is specified in the protocol, IB or SPC as not requiring immediate

reporting. All other adverse events should be reported on the regular progress/follow- up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the NWSTC immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the NWSTC as soon as possible. The initial report shall be followed by detailed, written reports.

ii. Send the SAE form by fax (within 24 hours or next working day) to the NWSTC.

Fax Number: 0151 794 8930/8931

iii. The responsible investigator must **notify** their local ethics committee (LREC) and R&D department of the event (as per standard local procedure).

iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

v. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the NWSTC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vi. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.9.1 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments unless criteria have been fulfilled (section 7.4) and unblinding has taken place. Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the clinical trials unit prior to reporting to the regulator and re-evaluated for expectedness in light of the administered treatment.

10.10 Responsibilities – LCTU

The NWSTC, part of LCTU, is undertaking duties delegated by the trial sponsor/, University of Liverpool, and is responsible for the reporting of SUSARs and other SARs to the Research Ethics Committee as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the NWSTC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.

- SUSARs that are not fatal or life-threatening must be reported within 15 days of the NWSTC first becoming aware of the reaction.

- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

VI. An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;

VII. Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;

VIII. New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:

- A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;

- A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;

- A major safety finding from a newly completed animal study (such as carcinogenicity).

- Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

IX. Recommendations of the independent members of Trial Steering Committee, if any, where relevant for the safety of the subjects.

Staff at the NWSTC will liaise with the designated Clinical Co-ordinator who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and REC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The NWSTC will also send an annual progress report to the Research Ethics Committee which will include all safety information.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

Ethical review of the study is a legal requirement to safeguard the rights, dignity and welfare of people participating in research. Amendments made to the study after a favourable ethical and regulatory opinion will be submitted and approved prior to implementation. The requirement for ethical and regulatory authority approvals applies to all participating countries. Each participating PI will be named on the original ethics application form or on a subsequent substantial amendment. Written evidence of favourable NHS capacity and capability must be made available to the NWSTC prior to randomisation of subjects at site.

Specifically for the DEFeND trial:

1) There will be no involvement of patients who are children or deemed to lack capacity. There are no additional hospital visits required.

2) Consent will be sought after a full explanation of the trial including potential risks and benefits. Consent will not be taken on the same day as their surgery.

3) The only additional investigation will be a wound swab. This is an entirely painless and non-invasive procedure with no associated risks.

4) There will be no use of placebo.

5) No patient will be denied any additional treatment.

11.2 Ethical Approval

The trial protocol has received the favourable opinion of the North West – Greater Manchester East Multi-centre Research Ethics Committee (MREC) but all participating sites must undergo site specific assessment of capacity and capability. A

copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to NWSTC before patients are entered. The NWSTC should receive a confirmation of capacity and capability for each new centre via the site's R&D department

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in NWSTC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient representative for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Study Discontinuation

The chief investigator can prematurely close this trial after consultation with the TSC. The local ethics committee will be informed. Reasons for trial termination include:

1. The incidence or severity of SAE's/morbidity in this trial indicates a potential health hazard caused by the study treatment.

2. External evidence demanding trial termination.

12 REGULATORY APPROVAL

This trial does not require regulatory approval as the MRHA do not consider DEFeND to be a clinical trial of an investigational medicinal product (CTIMP).

13 TRIAL MONITORING

Site monitoring is conducted to ensure protection of patients participating in the trial, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. Provide a description of how site monitoring will be conducted. A monitoring plan based on the risk assessment and in line with NWSTC Monitoring SOPs should be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

13.1 Risk Assessment

In accordance with the NWSTC Standard Operating Procedure a risk assessment will be completed in partnership with the following:

- Trial Sponsor
- Chief Investigator
- Trial Coordinator
- Trial Statistician

In conducting the risk assessment, the contributors will consider potential patient, organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment will be assigned according to the following categories:

1. Type A: no higher than that of standard medical care
2. Type B: somewhat higher than that of standard medical care
3. Type C: markedly higher than that of standard medical care

This trial is a Non-CTIMP and the risk categories described above for CTIMPs (type A, B or C) have been applied to the DEFeND trial.

As this is a surgical intervention trial comparing 'ARTISS' to 'no ARTISS', with no changes to the clinical procedure itself, this study is classed as Type A and thus will be of low risk.

13.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH E6, 1.51).

Original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial (ICH E6, 1.52):62.

In order to resolve possible discrepancies between information appearing in the (e)CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the (e)CRF. Data recorded in the (e)CRF should be consistent and verifiable with source data in source documents *other* than the (e)CRF (e.g. medical record, laboratory reports and nurses" notes). Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly in the (e)CRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the (e)CRF will be considered the **source document**, unless otherwise indicated by the investigator.

In addition to the above, date (s) of conducting informed consent including date of provision of patient information, trial screening number, trial number, study treatment and the fact that the patient is participating in a clinical trial should be added to the patients' medical record contemporaneously.

13.3 Data Capture Methods

All trial data will be captured using electronic Case Report Forms (eCRFs), transcribed to a MACRO Database. This database is designed and maintained by the NWSTC. The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded and all missing data must be explained.

All eCRFs are entered directly into a MACRO database that can be accessed via a secure webpage by research site staff and the relevant staff at NWSTC. The client application is secured with a unique username/password combination allocated to each delegated member of the research team. When data is entered into an eCRF it is electronically stamped with the date, time and the person who entered it. If data is changed on an eCRF, it is electronically stamped with the change and

will be accompanied with the date, time, person and a reason for making the change or correction. The previous value is recorded in an audit trail for each data item.

Each eCRF contains specific validation checks on the data being entered. If any values are outside what is expected, or data is missing, this is flagged up and will be raised as a discrepancy on the main database system. Regular reports will be generated to identify discrepancies in the data, and allow for follow up. Comprehensive guidelines for eCRF data entry will be provided to all staff who have been delegated the responsibility for data collection. Where the site is unable to upload data using the eCRF, e.g. internet unavailability, a backup paper CRF will be available to use and accessed from the NWSTC portal. In such cases the research staff will retrospectively enter the data onto the trial MACRO database following the visit.

13.4 Monitoring at North West Surgical Trials Centre

Data stored at NWSTC will be checked for missing or unusual values (range checks) and checked for consistency within patients over time. If any such problems are identified, they will be queried with the responsible site.

NWSTC will periodically send reminders for any overdue and missing data.

13.5 Clinical Site Monitoring

13.5.1 Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the participant's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

Participants will always be identified using only their unique trial identification number on the Case Report Forms and correspondence between the NWSTC and the participating site. Participants' will give their explicit consent for the NWSTC to be sent a copy of their consent form. This will be used to perform central monitoring of the consent process.

The Investigator must maintain documents not for submission to the NWSTC (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The NWSTC will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party. Representatives of the NWSTC and sponsor may be required to have access to

participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

13.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The DEFeND trial investigational sites and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities (national and foreign) or IEC. Such audits/inspections may take place at any site where trial related activity is taking place, the Sponsor's site(s), NWSTC or at any investigator's site.

As the main outcome of interest is surgical complications, graded according to the Clavien-Dindo classification, there is potential variation in how the severity of complication may be reported in the CRF. To ensure that the CRF accurately represents the clinical case notes, a blinded member of the research team will

regularly verify the source data and correlate the NHS case notes with the CRFs to ensure accuracy of data reporting.

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the NWSTC communication strategy for multicentre trials. This includes management system for the Green light process, conforming to the total Quality Management System currently operating within the NWSTC.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the Sponsor informs the investigator that the documents are no longer to be retained. In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the hospital or retires before the end of required storage period. Delegation must be documented in writing. The NWSTC undertakes to store originally completed (e)CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

Essential documents should be retained for at least 5 years after the completion of the trial. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the NWSTC to inform the investigator/institution as to when these documents no longer need to be retained.

At the point where it is decided that the trial documentation is no longer required; the Investigator will be responsible for the destruction of all site trial specific documentation and the Sponsor/NWSTC will be responsible for the destruction of all trial related materials retained by the Sponsor/NWSTC.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent forms being supplied to the NWSTC by recruiting centres. This requires that name data will be transferred to the NWSTC, which is explained in the PIS. The NWSTC will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14 INDEMNITY

DEFeND is sponsored by the University of Liverpool (sole sponsor) and co-ordinated by the NWSTC in the University of Liverpool. The University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

“A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process”.

15 FINANCIAL ARRANGEMENTS

DEFeND is a non-commercial, investigator-initiated and investigator-led trial. Patients recruited to the study may be reimbursed a maximum of £25 for travel costs incurred due to any extra hospital visits required specifically for the study. The trial is funded by the National Institute for Health Research, Research Doctoral Research Fellowship programme, consequently having automatic endorsement from the UK Clinical Research Network (UKCRN). This organisation will be responsible for providing local investigators with the necessary research infrastructure.

16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

The composition of the TMG is as follows.

Chief Investigator

Other lead investigators (clinical and non-clinical) Trial statistician

Speciality Trainees Trial Coordinator Data Manager

The role of the TMG is to monitor all day-to-day aspects of the conduct and progress of the trial, ensure the trial protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

The TMG will meet approximately 3 times a year.

The TMG will provide a recommendations to the TSC concerning any aspect of the trial.

A smaller TMG sub-group comprising of the Chief Investigator, Doctoral Research Fellow, Trial statistician and Trial Co-ordinator will meet on approximately a monthly basis to discuss trial management and progress.

16.2 Trial Steering Committee (TSC)

The composition of the TSC is as follows. Membership details are available from the Trial Coordinator.

Independent chairperson expert in the field of Head & Neck Surgery Independent expert in the field of Head & Neck Surgery, Independent statistician,

Principal Investigator (other than the CI) Patient representative

Chief Investigator Speciality Trainees Trial Statistician Trial Coordinator.

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent chairperson. The full role and responsibilities are stipulated within its Charter.

As no formal Independent Data and Safety Monitoring Committee (IDSMC) will be convened, all interim safety data will be reviewed by the independent members of the TSC (chairperson, expert and statistician). The ultimate decision for the continuation of the trial lies with the TSC.

The frequency of TSC meetings will be decided at the initial meeting. It is expected that they will occur at 6 monthly intervals, with the first meeting to be held prior to the recruitment of the first participant.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

No formal Independent Data and Safety Monitoring Committee (IDSMC) will be convened for this study. In keeping with the guidance outlined in the document 'Guideline in Data Monitoring Committees' published by the Committee for Medicinal Products for Human Use in 2005, it is thought that an IDSMC is not required. This is because patients will be treated for a very short period of time (single administration during surgery) and Fibrin Sealants are well characterised and already widely used within healthcare. Although there are potential risks to patients, these are incredibly rare and known.

The independent members of the Trial Steering Committee (Chairperson, expert, statistician) will take responsibility for reviewing all interim safety data. The independent members will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. Given this is a pilot/feasibility study, it is anticipated that the TSC will only recommend termination on grounds of safety.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

- **18.1 Version 1.0 (12/Feb/2018)**

Original Pre-approved version.

18.2 Version 2.0 (27/Jun/2018)

Change 1. Protocol

The addition of a patient reported outcome measure. This addition has been adopted from the 'Bluebelle' study and constitutes a wound healing questionnaire. Patient will be asked to complete this questionnaire only once before they exit the study. In order to validate the questionnaire for use in a future phase III trial clinicians will also complete a short 'face-to-face' assessment of surgical site infection at the last clinic visit. Both questionnaires have been added to Appendix D of the protocol.

Change 2. Protocol

Addition of ISRCTN number

Change 3. Protocol

Update figure 1 (p. 26) schedule of trial procedures. This was reviewed by research nurses who considered the original version confusing. It appeared as though patients required several assessments for rows 1-9 and "laboratory tests" rows

1-3 of the table when in fact these only needed to be done once before recruitment. The table has been changed to accommodate this.

Change 4. Protocol

North West - Greater Manchester East REC added to section 11.2

Change 5. Informed Consent Form

Addition of a clause asking patients whether they wish to consent to the taking of microbiology wound swabs for a sub-study.

Change 6. Participant Information Sheet & Summary Participant Information Sheet

Changes to inform patients of the additional wound healing questionnaire

Change 7. HRA Schedule of Events

The schedule of events has been updated to include the new wound healing questionnaire. Also ‘local recruiting surgeons’ will assess the blinding strategy in addition to ‘local research nurses’.

19 REFERENCES

1. Maillard J., Elia N., Haller C.S., Delhumeau C. & Walder B. (2015) Preoperative and early postoperative quality of life after major surgery - a prospective observational study. *Health Qual Life Outcomes*. 13**,** 12

2. Brown S.R., Mathew R., Keding A., Marshall H.C., Brown J.M. & Jayne D.G. (2014) The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Ann Surg*. 259**,** 916-923

3. Huang J., Barbera L., Brouwers M., Browman G. & Mackillop W.J. (2003) Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *J Clin Oncol*. 21**,** 555-563

4. Price G R.M., Wight R, Putnam G, Watson M (2011) Major surgical resections in England: head and neck cancers. Oxford Cancer Intelligence Unit, National Cancer Intelligence Network

5. Pellini R., Mercante G., Marchese C. *et al.* (2013) Predictive factors for postoperative wound complications after neck dissection. *Acta Otorhinolaryngol Ital*. 33, 16-22

6. Masud M.K., Ahmad S.M., Karim M.A. *et al.* (2014) Complications of neck dissection at a tertiary level hospital: study of 30 cases. *Mymensingh Med J*. 23, 658- 666

7. Mehanna H., Wong W.L., McConkey C.C. *et al.* (2016) PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. *N Engl J Med*. 374, 1444- 1454

8. VanderWalde N.A., Fleming M., Weiss J. & Chera B.S. (2013) Treatment of older patients with head and neck cancer: a review. *Oncologist*. 18, 568-578

9. Waters A.M., Tudur Smith C., Young B. & Jones T.M. (2014) The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer. *Trials*. 15, 168

10. Main B.G. (2016) Core information for informed consent in head and neck cancer surgery. In *School of Social and Community Medicine*. University of Bristol

11. Woods R.S., Woods J.F., Duignan E.S. & Timon C. (2014) Systematic review and meta-analysis of wound drains after thyroid surgery. *Br J Surg*. 101, 446-456

12. Bajwa M.S. T.-S.C., Shaw R.J., Schache A.G. (2017) Fibrin sealants in soft- tissue surgery of the head and neck: a systematic review and meta-analysis of randomised controlled trials. *Clinical Otolaryngology*. 42(6): 1141-52

13. Sajid M.S., Hutson K.H., Rapisarda I.F. & Bonomi R. (2013) Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery. *Cochrane Database Syst Rev***,** CD009557

14. Huang C.W., Wang C.C., Jiang R.S., Huang Y.C., Ho H.C. & Liu S.A. (2016) The impact of tissue glue in wound healing of head and neck patients undergoing neck dissection. *Eur Arch Otorhinolaryngol*. 273, 245-250

15. Vidal-Perez O., Flores-Siguenza L., Valentini M., Astudillo-Pombo E., Fernandez-Cruz L. & Garcia-Valdecasas J.C. (2016) [Application of fibrin sealant in patients operated on for differentiated thyroid cancer. What do we improve?]. *Cir Cir*. 84, 282-287

16. Kaur G., Hutchison I., Mehanna H., Williamson P., Shaw R. & Tudur Smith C. (2013) Barriers to recruitment for surgical trials in head and neck oncology: a survey of trial investigators. *BMJ Open*. 3(4). pii: e002625

17. Agrama M.T., Reiter D., Cunnane M.F., Topham A. & Keane W.M. (2003) Nodal yield in neck dissection and the likelihood of metastases. *Otolaryngol Head Neck Surg*. 128, 185-190

18. Taylor R.J., Chepeha J.C., Teknos T.N. *et al.* (2002) Development and validation of the neck dissection impairment index: a quality of life measure. *Arch Otolaryngol Head Neck Surg*. 128, 44-49

19. Parikh S., Tedman B.M., Scott B., Lowe D. & Rogers S.N. (2012) A double blind randomised trial of IIb or not IIb neck dissections on electromyography, clinical examination, and questionnaire-based outcomes: a feasibility study. *Br J Oral Maxillofac Surg*. 50, 394-403

20. Dindo D., Demartines N. & Clavien P.A. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 240, 205-213

Appendix E: ARTISS Product Information Sheets

ARTISS Solutions for Sealant

Summary of Product Characteristics Updated 18-Nov-2015 | Baxter Healthcare Ltd

1. Name of the medicinal product ARTISS Solutions for Sealant Deep frozen

2. Qualitative and quantitative composition

Component 1:

Sealer Protein Solution

Human Fibrinogen (as clottable protein)	91 mg1/ml
Aprotinin (synthetic)	3000 KIU2/ml

Component 2:

Thrombin Solution

Human Thrombin	4 IU3/ml
Calcium Chloride	40 µmol/ml

1 prefilled double chamber syringe which contains Sealer Protein Solution (with Aprotinin), deep frozen <1 ml><2 ml><5 ml>, in one chamber and Thrombin Solution (with Calcium Chloride), deep frozen<1 ml><2 ml><5 ml>, in the other chamber results in <2 ml><4 ml><10 ml> total volume of product ready for use.

After mixing	1 ml	2 ml	4 ml	10 ml
Component 1: Sealer protein solution Human Fibrinogen (as clottable protein) Aprotinin (synthetic)	45.5 mg 1,500 KIU	91 mg 3,000 KIU	182 mg 6,000 KIU	455 mg 15,000 KIU
Component 2: Thrombin Solution Human Thrombin Calcium Chloride	2 IU 20 µmol	4 IU 40 µmol	8 IU 80 µmol	20 IU 200 µmol

ARTISS contains Human Factor XIII co-purified with Human Fibrinogen in a range of 0.6 – 5 IU/ml.

For the full list of excipients, see section 6.1.

1 Contained in a total protein concentration of 96 - 125 mg/ml

2 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)

3 Thrombin activity is calculated using the current WHO International Standard for Thrombin.

3. Pharmaceutical form Solutions for Sealant Deep frozen

Colourless to pale yellow and clear to slightly turbid solutions. Component 1, Sealer Protein Solution: pH 6.5 – 8.0 Component 2, Thrombin Solution: pH 6.0 – 8.0

4. Clinical particulars

4.1 Therapeutic indications

ARTISS is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples (see 5.1). In addition, ARTISS is indicated as an adjunct to hemostasis on subcutaneous tissue surfaces.

4.2 Posology and method of administration

ARTISS is intended for hospital use only. The use of ARTISS is restricted to experienced surgeons who have been trained in the use of ARTISS.

Posology

The amount of ARTISS to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.2-12 ml. For some procedures (e.g. the sealing of large burned surfaces), larger volumes may be required.

The initial amount of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary, to any small areas that may have not been previously treated.

However, avoid reapplication of ARTISS to a pre-existing polymerized ARTISS layer as ARTISS will not adhere to a polymerized layer.

It is recommended that the initial application covers the entire intended application area.

As a guideline for the gluing of surfaces, 1 pack of ARTISS 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm2.

The skin graft should be attached to the wound bed immediately after ARTISS has been applied. The surgeon has up to 60 seconds to manipulate and position the graft prior to polymerization. After the flap or graft has been positioned, hold in the desired position by gentle compression for at least 3 minutes to ensure ARTISS sets properly and the graft or flap adheres firmly to the underlying tissue.

The required amount of ARTISS depends on the size of the surface to be covered. The approximate surface areas covered by each pack size of ARTISS by spray application are:

Approximate area requiring tissue adherence	Required pack size of ARTISS

100 cm2	2 ml
200 cm2	4 ml
500 cm2	10 ml

To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the mixed Sealer Protein - Thrombin Solution should be applied.

ARTISS has not been administered to patients > 65 years old in clinical trials.

Paediatric Population

Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

For epilesional (topical) use. Do not inject.

For subcutaneous use only. ARTISS is not recommended for laparoscopic surgery.

In order to ensure optimal safe use of ARTISS it should be sprayed using a pressure regulator device that delivers a maximum pressure of up to 2.0 bar (28.5 psi).

Prior to applying ARTISS the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

ARTISS must be sprayed only onto application sites that are visible.

ARTISS should only be reconstituted and administered according to the instructions and with the devices recommended for this product (see section 6.6).

For spray application, see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure and length of applicator tips.

4.3 Contraindications

ARTISS is not indicated to replace skin sutures intended to close surgical wounds.

ARTISS alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.

ARTISS must never be applied intravascularly.

ARTISS is contraindicated in the case of hypersensitivity to the active substances or to any of the excipients (see also section 4.4. Special Warnings).

4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly. Life threatening thromboembolic complications may occur if the preparation is applied intravascularly. Soft tissue injection of ARTISS carries the risk of local tissue damage.

Caution must be used when applying fibrin sealant using pressurized air or gas.

- Any application of pressurized air or gas is associated with a potential risk of air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening or fatal.

- **Apply ARTISS as a thin layer. Excessive clot thickness may negatively interfere with the product´s efficacy and the wound healing process.**

- **Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO2 and therefore cannot be excluded with ARTISS when sprayed in open wound surgery.**

- **When applying ARTISS using a spray device, be sure to use a pressure within the pressure range recommended by the spray device manufacturer (see table in section 6.6 for pressures and distances).**

- **ARTISS spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer. Do not spray closer than the recommended distances.**

- **When spraying ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO2 should be monitored because of the possibility of occurrence of air or gas embolism (also see section 4.2).**

- ARTISS must not be used with the Easy Spray / Spray Set system in enclosed body areas.

- Only use application devices CE marked for the administration of ARTISS.

ARTISS is not indicated for hemostasis and sealing in situations where a fast clotting of the sealant is required. Especially in cardiovascular procedures in which sealing of vascular anastomoses is intended ARTISS should not be used.

ARTISS is not indicated for use in neurosurgery and as a suture support for gastrointestinal anastomoses or vascular anastomoses as no data are available to support these indications.

Before administration of ARTISS care is to be taken that parts of the body outside the designated application area are sufficiently protected/covered to prevent tissue adhesion at undesired sites.

Oxycellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials (see Section 6.2).

As with any protein-containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration must be discontinued immediately.

ARTISS contains aprotinin. Even in case of strict local application, there is a risk of anaphylactic reaction linked to the presence of aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records.

As synthetic aprotinin is structurally identical to bovine aprotinin the use of ARTISS in patients with allergies to bovine proteins should be carefully evaluated.

In the event of anaphylactic/anaphylactoid or severe hypersensitivity reactions, administration is to be discontinued. If possible, remove any applied, polymerized product from the surgical site. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction. State-of-the-art emergency measures are to be taken. In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual

donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemolytic anemia).

It is strongly recommended that every time that ARTISS is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

Similar to comparable products or thrombin solutions, the product is denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

See section 4,4 or 6.2 for substances that can interfere with the product's performance.

4.6 Fertility, pregnancy and lactation

The safety of fibrin sealants/haemostatics for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Animal studies have also not been performed.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

See section 4.4 for information on Parvovirus B19 infection. The effects of ARTISS on fertility have not been established.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Intravascular injection could lead to thromboembolic events and disseminated intravascular coagulation (DIC) and there is also a risk of anaphylactic reactions (see section 4.4).

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/hemostatics.

In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin (see section 4.4) or any other constituents of the product.

Even if a first treatment with ARTISS was well tolerated, a subsequent administration of ARTISS or systemic administration of aprotinin may result in severe anaphylactic reactions.

Antibodies against components of fibrin sealant may rarely occur. For safety with respect to transmissible agents, see section 4.4.

Life threatening/fatal air or gas embolism when using devices with pressurized air or gas occurred; this event appears to be related to an inappropriate use of the spray device (e.g. at higher than recommended pressures and in close proximity of the tissue surface).

Adverse reactions summarized in the table below were reported from clinical studies of ARTISS and from post-marketing experience with Baxter Fibrin Sealants (marked with a p in the adverse event table). Known frequencies of these adverse reactions are based on a controlled clinical study in 138 patients where skin grafts were fixed to excised burn wounds using ARTISS. None of the events observed in the clinical study were classified as serious.

The ADRs and their frequencies are summarized below:

Common (≥1/100 to <1/10) Uncommon (≥1/1000 to <1/100)

Not known (cannot be estimated from the available data)

Table 1

Adverse Reactions

System organ class (SOC)	**Preferred MedDRA Term**	**Frequency**
Skin and subcutaneous tissue disorders	Dermal cyst	uncommon
	Pruritus	common
Injury, poisoning and procedural complications	Skin graft failure	common

Vascular disorders	Air embolismp due to an inappropriate use of the spray device (see section 4.4)	not known

p Adverse events observed in post-marketing experience with Baxter Fibrin Sealants.

Class Reactions

Other adverse reactions associated with products of the fibrin sealant/hemostatic class include: Hypersensitivity reactions which could manifest as application site irritation, chest discomfort, chills, headache, lethargy, restlessness and vomiting. Further class reactions are: Anaphylactic reaction, bradycardia, tachycardia, hypotension, haematoma, dyspnoea, nausea, urticaria, flushing, impaired healing, oedema, pyrexia and seroma.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No case of overdose has been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics, ATC code: B02BC; tissue adhesives, ATC code: V03A K

ARTISS can replace sutures or staples when used for fixation of skin grafts to burned or otherwise injured wound areas. ARTISS can be used as an adjunct to sutures or staples to adhere and seal skin flaps in cases where sutures/staples are expected to yield unsatisfactory results with respect to postoperative hematoma or seroma formation.

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for the conversion of fibrinogen and the crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by anti-fibrinolytics. Aprotinin is present in ARTISS (frozen) as an antifibrinolytic to prevent premature degradation of the clot.

For efficacy, *in vivo* studies in an animal model closely imitating the situation in patients were used. ARTISS (frozen and lyophilized presentations) demonstrated efficacy regarding sealing autologous split skin grafts and mesh grafts.

ARTISS (frozen) was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomised, controlled, multicenter clinical study. In each of the 138 patients, two comparable test sites were identified. In one test site the skin graft was fixed with ARTISS in the other test site the graft was fixed with staples (control). ARTISS proved to be non-inferior to staples with respect to the primary efficacy endpoint, complete wound closure at Day 28 was evaluated by a blinded evaluator panel from photographs. This was achieved in 55/127 patients (43.3%) treated with ARTISS (frozen) and 47/127 patients (37%) treated with staples.

With respect to secondary endpoints, ARTISS showed a significantly lower incidence and size of hematoma/seroma on Day 1 ($p < 0.0001$ for incidence as well as size). Incidence and area of engraftment on Day 5 and wound closure on Day

14, as well as area of wound closure on Day 28 were not different. ARTISS was also superior to staples with respect to patient satisfaction ($p < 0.0001$) and patients experienced significantly less anxiety about pain with ARTISS than with staples ($p < 0.0001$). Moreover, ARTISS was significantly superior to staples with respect to the investigator's assessment of quality of graft adherence, preference of fixation method and satisfaction with graft fixation, overall quality of healing and overall rate of healing ($p < 0.0001$).

Thirty-seven (37) pediatric patients aged 1.1 to 18 years were evaluated in this trial. Eighteen (18) of these patients were 6 years old or younger.

Dosage used in clinical trials was the same for pediatric and adult patients.

5.2 Pharmacokinetic properties

ARTISS is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Pharmacokinetic studies in different species of laboratory animals were not conducted.

Fibrin sealants/hemostatics are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

No preclinical safety data are available for ARTISS (thrombin 4 IU/ml). Toxicity studies were done with Fibrin Sealants containing thrombin 500 IU/ml, as representative for products containing thrombin 4 IU/ml. Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of Fibrin Sealant VH S/D (500 IU/ml). Fibrin Sealant VH S/D (500 IU/ml) also proved well tolerated in wound healing models in rats and rabbits, and in in vitro human fibroblast cultures.

6. Pharmaceutical particulars

6.1 List of excipients

Component 1: Sealer Protein Solution Human Albumin Solution

L-Histidine Niacinamide

Polysorbate 80 (Tween 80) Sodium Citrate Dihydrate Water for Injections

Component 2: Thrombin Solution Human Albumin Solution

Sodium Chloride Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Oxycellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store and transport frozen (at ≤ -20°C).

Keep the syringe in the outer carton in order to protect from light.

Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25°C). Do not refreeze or refrigerate after thawing.

6.5 Nature and contents of container

1 ml, 2 ml, or 5 ml of sealer protein solution and 1, 2 or 5 ml of Thrombin Solution in a single- use double-chamber syringe (polypropylene) with a tip-cap in a bag , and one device set with one double syringe plunger, 2 joining pieces and 4 application cannulae.

Pack size of 1 (1 x 1 ml + 1 ml, 1 x 2 ml + 2 ml, 1 x 5 ml + 5 ml)

Both Sealer Protein Solution and Thrombin Solution are contained in a single-use double- chamber syringe made of polypropylene.

Not all pack sizes may be marketed.

Other accessories for application of the product can be obtained from BAXTER.

6.6 Special precautions for disposal and other handling General

To prevent ARTISS from adhering to gloves and instruments, wet these with sodium chloride solution before contact.

As a guideline for the gluing of surfaces, 1 pack of ARTISS 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm2.

The required dose of ARTISS depends on the size of the surface to be covered.

Handling and Preparation

The inner bag and its contents are sterile unless the integrity of the outside package is compromised.

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. (In order to control the specified temperature range, the water temperature should be monitored using a thermometer and the water should be changed as necessary. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum-coated plastic bags.)

The protective syringe cap should not be removed until thawing is complete and the joining piece is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

Thaw pre-filled syringes using one of the following options:

1. Room Temperature Thawing (not exceeding +25°C):

The product can be thawed at room temperature. Times given in Table 1 are minimum times for thawing at room temperature. The maximum time the product can be kept (in both aluminum-coated plastic bags) at room temperature is 14 days.

When thawing at room temperature, the product must be additionally warmed to 33°C – 37°C in an incubator just before use. Respective warming times in the incubator are also given in Table 1.

Table 1: Thawing times at Room Temperature (= RT) followed by additional warming, prior to use, in an Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing Times at Room Temperature (Product in aluminum-coated plastic bags)		Warming Times at 33-37°C in Incubator after Thawing at RT (Product in aluminum-coated plastic bags)
2 ml	60 minutes	+	15 minutes

4 ml	110 minutes	+	25 minutes
10 ml	160 minutes	+	35 minutes

Once ARTISS has been warmed up to 33 – 37°C the product may be stored for up to 4 hours.

2. Quick Thawing:

Table 2: Thawing and Warming Times with Sterile Water Bath at 33°C to a maximum of 37°C

Transfer plunger and the inner pouch to the sterile field, remove prefilled syringe from inner pouch and place directly into sterile water bath. Ensure the contents of the prefilled syringe are completely immersed in water.

Pack Size	Thawing and Warming Times (Product removed from aluminum-coated plastic bags)
2 ml	5 minutes
4 ml	5 minutes
10 ml	12 minutes

A third alternative is to thaw the product off the sterile field using a non-sterile water bath.

Maintain the prefilled syringe in both pouches and place into a water bath off the sterile field for an appropriate time (see Table 3). Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch with prefilled syringe and plunger to the sterile field.

Table 3: Thawing and Warming times off the Sterile Field with Non-Sterile Water Bath at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times (Product in aluminum-coated plastic bags)
2 ml	30 minutes
4 ml	40 minutes
10 ml	80 minutes

Alternatively, the sealant components may be thawed and warmed in an incubator between 33°C and 37°C. The thawing and warming times in the incubator are indicated in Table 4 below. The times refer to product in the aluminum-coated plastic bags.

Table 4: Thawing and Warming Times in Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times in Incubator (Product in aluminum-coated plastic bags)
2 ml	40 minutes
4 ml	85 minutes

10 ml 105 minutes

Note: Do not thaw by holding product in your hands. Do not microwave.

After thawing do not refrigerate or refreeze.

After Quick Thawing (i.e. thawing at a temperature of 33 – 37°C) ARTISS may be stored at 33

– 37°C for a maximum of 4 hours.

To facilitate optimal blending of the two solutions, the two sealant components must be warmed to 33 – 37°C immediately before use. (The temperature of 37°C must, however, not be exceeded!)

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration or any variation in physical appearance. In the event of either being observed, discard the solution.

The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (e.g., due to an interruption of the cold storage chain or by overheating during warming). In this case, ARTISS must not be used.

Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25°C). If not used within 14 days after thawing, ARTISS has to be discarded.

The protective syringe cap should not be removed until thawing is complete and the joining piece is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

For further preparation instructions please refer to the responsible nurse or medical doctor.

ADMINISTRATION

For application, the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution has to be connected to a joining piece and an application cannula as provided in the accompanying set of devices. The common plunger of the double-chamber syringe ensures that equal volumes are fed through the joining piece before being mixed in the application cannula and ejected.

Operating Instructions

- Connect the nozzles of the double-chamber syringe to the joining piece ensuring that they are firmly fixed. Secure the joining piece by fastening the tether strap to the double-chamber syringe. If the tether strap tears, use the spare joining piece. If none is available, further use is still possible but tightness of the connection needs to be ensured to prevent any risk of leaking.

- Fit an application cannula onto the joining piece.

- Do not expel the air remaining inside the joining piece or application cannula until you start actual application as the aperture of the cannula may clog otherwise.

- Immediately before application expel and discard the first several drops from the application cannula to ensure adequately mixed product

- Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

If application of the fibrin sealant components is interrupted, clogging may occur in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g. minimally invasive surgery, application to large or difficult-to-access areas.

When using these application devices, strictly follow the Instructions for Use of the devices.

Spray application

When applying ARTISS using a spray device be sure to use a pressure and a distance from tissue within the ranges recommended by the manufacturer as follows:

Recommended pressure, distance and devices for spray application of ARTISS					
	Spray set to be used	Applicator tips to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open wound surgery of subcutaneous tissue	Tisseel / Artiss Spray Set	n.a.	EasySpray	10 – 15 cm	1.5-2.0 bar (21.5-28.5 psi)
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		

When spraying the ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO2 should be monitored because of the possibility of occurrence of air or gas embolism (see sections 4.2 and 4.4).

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Baxter Healthcare Ltd Caxton Way

Thetford Norfolk IP24 3SE

United Kingdom

8. Marketing authorisation number(s)

PL00116/0634

9. Date of first authorisation/renewal of the authorisation

11/03/2009

10. Date of revision of the text

06/11/15

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A.2 Patient Information Sheet (PIS)

IRAS Number: 234851

PATIENT INFORMATION SHEET

Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

You have been invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- **Part One** tells you the purpose of the study and what will happen to you if you take part.
- **Part Two** gives you more detailed information about the conduct of the study.

The clinical team in charge of your care will go through the details with you, but please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Part One

What is the purpose of the study?

A neck dissection is an operation to remove the glands in the neck either because they have cancer in them or they are at risk of cancer spreading to them. Complications after neck dissection can be a significant problem for patients and may affect their quality of life.

Research on understanding the feelings of patients who have had head and neck cancer treatment, has shown that avoiding complications is very important. We have found evidence that by giving patients a substance that copies the blood clotting process called Fibrin Sealant, we may be able to protect them from complications. This is because this substance can seal areas of bleeding and stick the raw surfaces of the wound together, reducing the space for blood to collect in. Fibrin Sealants are natural products derived from the same human blood that is used for blood transfusions and are sprayed directly into the wound. Unfortunately, there is no high quality research that has been able to answer whether Fibrin

Sealants can prevent complications after neck dissection. Therefore we have designed a clinical trial to help us answer this important question. However, before this can be started we need to conduct a miniature version of the trial (pilot study) to make sure it has been designed in the best possible way. Please be aware that this information sheet is for the pilot study and not the full trial. With your help we will be able to improve the design of our future trial to make sure we can find out whether or not Fibrin Sealants can really help avoid complications.

Why have I been chosen?

You were chosen to take part in this study because the team of surgeons and doctors looking after you think that you may require a neck dissection (an operation to remove the glands in your neck). We will be asking all patients who are due to have a neck dissection and meet our criteria for being involved in the study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be asked to sign a consent form but you are free to withdraw at any time. If you do decide not to take part or withdraw from the study we will be very interested to understand your reasons, however you do not have to disclose this information. **A decision not to take part, or a decision to withdraw at any time will not affect the standard of care you receive**.

What will happen to me if I take part?

If you decide to take part, you will receive all of your treatment as normal. The only differences will be:

1. Before the operation you will be asked to complete a very short questionnaire regarding neck and shoulder function.
2. If you are a woman of childbearing age, you will be offered a pregnancy test. If you are found to be pregnant you will not be allowed to take part in the study.
3. During the operation and in the days following your operation the nurse will lightly wipe your neck and mouth with a cotton buds. This will be used to grow bacteria in a laboratory (University of Liverpool) to increase our understanding of infections after surgery and will not be painful. If you do not wish to have this extra test you can still take part in the rest of the study.
4. At the end of your operation (just before the surgeon starts stitching the wound back together) you will be randomly allocated to either have the Fibrin Sealant sprayed into your wound or not. There is a 50:50 chance you will receive the Fibrin Sealant. Both you and the nurses looking after you will not be told whether you have had the Fibrin Sealant. After the operation you will return to the ward and the doctors and nurses will work hard to get you better as they normally do.
5. Once you have been discharged home, you will need to come back to hospital 1 – 2 weeks later. During this appointment your wounds will be assessed and any stitches/clips removed. The nurse will also take some more cotton buds of your neck wound and mouth.
6. If you need to attend any unscheduled hospital appointments because of a problem/complication, you will need to inform the research team (telephone number on page 5).

7. During an appointment 4 – 6 weeks after the surgery you will re-take the short questionnaire you took before the surgery regarding neck and shoulder function as well as another questionnaire asking you about wound healing and infection. In addition to this you will be asked whether or not you think you received the Fibrin Sealant during your operation and how certain you are of this. This is so we can assess how good we were at keeping it a secret from you. You will also be asked how much benefit the Fibrin Sealant would need to provide before you would consider recommending it to future patients. After this appointment you will exit the study and carry on with the same care that everyone else, who is not in the study, receives.

What do I have to do?

If you take part in this study:

1. You will be asked to take some very short questionnaires before your surgery and at 4 – 6 weeks after your surgery (see points 1 and 7 above).
2. You will need to attend 2 hospital appointments after your surgery. The first 1 – 2 weeks after surgery and the second 4 – 6 weeks after surgery.
3. If you need to attend any unscheduled hospital appointments because of a problem you will need to contact the research team (telephone number on page 5).

Everything else will be done for you and you don't need to take any extra drugs or medicines. There are no restrictions on any further treatment you may need after the surgery. The only extra test will be the cotton bud test to check for bacteria in your mouth and neck but you do not have to agree to this extra test. If you need to attend an extra hospital appointment purely for this research, reasonable travel expenses will be reimbursed.

What is being tested?

Fibrin Sealants are products that are derived from human blood that is used for blood transfusions. They are already being sold on the market and are approved and licenced for use in patients. They work by copying the clotting process and by forming a glue that seals leaking blood vessels and sticks the raw surfaces of the wound together. There is a 50:50 chance that you will have Fibrin Sealant sprayed inside the wound just before the surgeon stitches it back together while you are under anaesthetic. If you do receive the Fibrin Sealant it will only be sprayed once during your surgery.

What are the alternatives for treatment?

The alternatives for treatment are to have your surgery without the Fibrin Sealant.

What are the possible disadvantages and risks of taking part?

Taking part in this study will not have an effect on your cancer treatment. You will not be restricted in taking any drugs you may need or in having any further treatment.

Fibrin Sealants are considered to be very safe products and serious risks are very rare. The manufacturer reports the following potential risks:

1. **Itchiness** of the skin of the neck (between 1 – 10 patients out of a hundred). If you experience itchiness your doctor may treat this with antihistamines (allergy medicines) depending on how problematic this is for you.

2. **Fluid collection** under skin (less than 1 patient out of a hundred). Most fluid collections do not require treatment as your body will eventually absorb the fluid. If the fluid collection is large or problematic, your doctor may drain the fluid. This may be done by either drawing the fluid out using a syringe or formally opening the wound and letting the fluid out.

3. **Severe allergic reaction** (less than 1 patient out of a hundred). If you develop a severe allergic reaction it will normally develop during or immediately after the surgery. If signs and symptoms of allergy are noted you will receive treatment as a matter of urgency.

4. If the surgeon holds the spray too close to the blood vessels in your neck, air may enter the blood vessel causing a serious complication known as an **"air embolism"**. Patients who get "air embolisms" are at increased risk of heart attacks, strokes and breathing problems. Fortunately this is very rare as there have only ever been **6 reported cases** of life threatening "air embolism" out of many thousands of patients who have already been given Fibrin Sealants over the years. There have been no reported cases of "air embolism" from the type of Fibrin Sealant we intend to use (ARTISS, Baxter Healthcare LTD). **Every surgeon who uses the fibrin sealant in this study will be trained on how to avoid this complication**.

5. Because the Fibrin Sealant is taken from human blood that is used in blood transfusions, there is a **theoretical risk** of catching a **blood borne virus** (e.g. Hepatitis or HIV). People who donate their blood are always carefully selected to minimise the risk of transmitting viruses. Also the Fibrin Sealant has been carefully checked and treated to prevent contamination with viruses. Despite these efforts, we cannot guarantee that the Fibrin Sealant is free of viruses. There have been **no reported cases** of patients catching viruses from Fibrin Sealants in the scientific literature. In the very unlikely event that you do catch a virus, you will be referred to a specialist for treatment.

What are the possible benefits of taking part?

There are no specific benefits to taking part other than giving you the opportunity to take part in surgical research. The study has been designed to minimise extra tests and hospital visits so that your participation is as easy for you as possible.

Surgeons up and down the country are already using Fibrin Sealants however this is not based on high quality evidence. By participating in this pilot study, you will be helping us to design a 'full' trial that is as effective and efficient as possible. We hope that the 'full' trial will enable us to answer whether or not Fibrin Sealants are beneficial to patients undergoing neck dissection surgery.

Will my taking part in this study be kept confidential?

Yes. All the confidential information about your participation in this study will be treated as so. The detailed information on this is given in Part 2.

What if I wish to make a complaint?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you wish to raise some informal concerns or complaints please contact the Research Team (contact details below). If you wish to make a formal complaint about any aspect of this study please do this through the University of Liverpool Research Integrity and Governance Manager (contact details below). Further details on the complaints procedure can be found in Part Two under *"what if there is a problem?"*

For further information please contact the Research Team:

Appropriate job title:

[Trust to insert contact details]

Contact Number is:

[Trust to insert contact details]

For any complaints please contact the Research Integrity and Governance Manager:

Research Integrity and Governance Manager
Research Support Office
University of Liverpool / Liverpool Joint Research Office
2nd Floor Block D Waterhouse Building
3 Brownlow Street
Liverpool L69 3GL

Tel: 0151 794 8373
Email: sponsor@liverpool.ac.uk

This completes Part One of the Information Sheet. If the information in Part One has interested you and you are considering participation, please continue to read the additional information in Part Two before making any decision.

Part Two

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

If you no longer wish to take part in the study you can withdraw your consent at any time. We would ask that you contact us using the contact details written at the end of section one. We would be very interested to understand why you decided to withdraw from the study but you do not have to tell us. Any feedback you provide will be confidential and only used to try to improve the way the study is run.

Once you have left the study you will simply carry on with the treatment and hospital appointments that patients who are not involved in the study will receive. Regarding the information and samples we collected for the study, it is your choice if we keep them or discard them securely. We will clarify this with you at the time. Any safety information collected (complications that occur after surgery) however cannot be discarded and will be used.

What if there is a problem?

If you have a concern about any aspect of this study, you may speak with the Research Team at your hospital (contact details at end of Part One) who will do their best to answer your questions. If they are unable to answer your question, they may wish to escalate the query to the Chief Investigator or North West Surgical Trials Centre (University of Liverpool) who are responsible for overseeing the study. If you remain unhappy and wish to complain formally, you can do this through the University of Liverpool's Research Integrity and Governance Manager (contact details at end of Part One)

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated, but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you (if appropriate).

In the event of defective product then you may have grounds for a legal action for compensation against the manufacturer, but you may have to pay for your legal costs.

Will my taking part in this study be kept confidential?

If you join the study, some relevant parts of your medical records and the data collected for the study will be looked at by authorised persons from the North West Surgical Trials Centre (University of Liverpool) or their collaborators who are also involved in organising this research project. Data may also be looked at by representatives of regulatory authorities and by authorised people from the Trust or other NHS bodies to check that the study is being carried out correctly. **All will have a duty of confidentiality to you as a research participant**.

A scanned copy of your completed consent form will be securely uploaded to the North West Surgical Trials Centre (University of Liverpool) portal. Only delegated members of the research team will have access to this portal. The uploaded consent form will be checked by the Trial Manager based at the University of Liverpool to ensure it has been completed correctly. Once this check has been performed the electronic copy of your consent form will be permanently deleted. This means that the hospital that is treating you will hold your original consent form and no other copies will be stored elsewhere.

Hard copies of your consent form and any other hard copies of data collected for this study will be stored in your medical records. No hard copies of your data will be stored at the University of Liverpool. The electronic research data gathered will contain your initials, date of birth and NHS number. This research data will be stored for 15 years within a secure file held within the University of Liverpool.

Involvement of the General Practitioner/Family Doctor (GP)

With your consent, your GP will be informed of your involvement in the study. Any other medical practitioners who treat you, should you be admitted to hospital for any reason, will also be informed.

What will happen to any samples I give?

With your permission, we would like to transfer cotton bud swabs of your mouth and wound to the University of Liverpool for storage. These samples will be used only for investigating surgical infections and will not be used for any commercial purposes.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

Your sample will be coded and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good reason to do so. We will maintain this information so that we can properly manage the samples donated. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

All of your samples will be destroyed at the end of the study

Will any genetic tests be done?

Only on the bacteria that we grow from your wound swab. We will not carry out any genetic tests on human tissue.

What will happen to the results of the research study?

It is intended that once the study is complete a report will be written and the results will be published to make them available to the public. You will not be named or identified in any publication.

What rights do I have to the results of the research?

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form you do not give up any rights that you would otherwise have as a participant in research.

Who is organising and funding the research?

The research is being organised by the North West Surgical Trials Centre which is part of the University of Liverpool in collaboration with Aintree University Hospital in Liverpool. The research is being funded by the National Institute of Health Research which is part of the Department of Health (UK). The data collected in this study will contribute towards a PhD for a student based in the University of Liverpool.

Your doctor will <u>not</u> receive any payment for including you in this study.

Who has reviewed the study?

The study has been reviewed for scientific content by members of the **North West – Greater Manchester East Research Ethics Committee**.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

A.3 Informed Consent Form (ICF)

IRAS number: 234851

(To be printed on Hospital Trust headed paper)

PATIENT CONSENT FORM (please read carefully)

Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection:

A randomised external pilot trial

Name of Researcher:_____

Please initial each box

1. I confirm that I have read and understand the patient information sheet date: …… (Version: .....) describing the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records ☐

4. I agree to allow my General Practitioner and any other relevant medical practitioner to be informed of my involvement in the study. ☐

5. I agree for a copy of this completed consent form to be sent to the Liverpool Cancer Trial Unit (where it will be kept in a secure location), to allow confirmation that my consent for the trial has been given ☐

6. I agree to take part in the above study ☐

7. I understand that information held by the NHS and records maintained by the NHS Information Centre may be used to keep in touch with me and follow-up my health status. ☐

8. I give permission for swabs to be taken from my mouth and neck wound and transferred to the University of Liverpool for research into the prevention and treatment of infections. I understand that nobody outside of the study will have access to them and that they will be destroyed at the end of the study. ☐

A.4 GP Letter

<<Insert senders name and address>>

<<Insert recipient name and address>>

<<Insert date>>

Re: Patient inclusion in clinical trial – DEFeND: Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

Dear Dr <<insert GP name >>,

Patient name: … <<Insert Patient Name >>……

Date of Birth: … <<Insert Patient DOB>>……

NHS Number: … <<Insert Patient NHS Number>>……

After giving written informed consent, the above patient has been entered into a clinical trial. Please find enclosed a copy of the Patient Information Sheet (PIS) for the study containing all the relevant information.

DEFeND is a randomised multicentre pilot study to assess whether the application of Fibrin Sealant to the surgical wound reduces the rate of complications compared to 'standard of care' surgery without Fibrin Sealant.

Your patient will be randomised to have their neck dissection surgery either with Fibrin Sealant or without. This is a blinded trial which means your patient will not be told whether they received the Fibrin Sealant or not.

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr _____ at _____ (Hospital)

Tel: _____

Yours sincerely,

<<Insert PI Name and details>>
Enc. Patient information sheet

A.5 Risk Assessment

Liverpool Cancer Trials Unit: Risk Assessment Form

SECTION 1 – Sponsorship and Research Governance Risk Assessment This section should be completed and reviewed by the Trial Research Team and Study Sponsors			
Project Acronym:	DEFeND	**Full Name of Project**	**Determining the Effectiveness of Fibrin Sealants in R ducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial**
Chief Investigator (CI):	Andrew Schache	**Employer of CI:**	University of Liverpool
Trial of IMP/intervention:	Surgical Intervention: Neck dissection and Artiss Fibrin Sealant (non-CTIMP)	**Proposed Sponsor(s):**	University of Liverpool
Date of Sponsorship and Research Governance Risk Assessment:	29/08/2018		

Risk/Hazard identified	**Likelihood (Low,Medium or High)**	**Impact (Low, Medium or High)**	**Concerns and Recommendations for m gation and management**
Non-compliance with regulations	**L**	**M**	The MHRA has deemed this study to be a r CTIMP trial. The sponsor, and delegated others, will nee assure compliance with the NHS Research G ernance Framework, putting the appropr Quality Assurance (QA) measures in pl

			Sponsor audits will be performed in accorda with their standard operating proced (SOPs). The Liverpool Cancer Trials Unit's (LCTU) Qu System has been developed to facilitate con ance with the regulations. This trial has been veloped and will be managed by the LCTU Q ity System and will be subject to the interna dit programme
Unclear accountability of organisations involved	**M**	**L**	Sponsorship is confirmed by: University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 794 8739 Email: sponsor@liv.ac.uk A Clinical Trial Site Agreement (including a terial Transfer Agreement) will be prepared signed by each recruiting site, the Sponso and the University of Liverpool.

			Clear LCTU SOPs/plans describing trial pr dures must in place as part of the LCTU st green light checklist.
Risk/Hazard identified	**Likelihood (Low,Medium or High)**	**Impact (Low, Medium or High)**	**Concerns and Recommendations for m gation and management**
Inadequate/poorly documented delegation to sites	**L**	**M**	Recruiting sites: Principal Investigators at cruiting sites will be take responsibility for delegation of roles to the research team firming each member 'has been adequa trained on the current protocol for this trial' GCP certificates and curriculum vitae of t members will be held on the site trial file and delegation log will be signed by both the PI the team member specifying the roles they delegated to do.
Poor quality control and quality assurance	**L**	**M**	**LCTU:** There will be regular internal audit of LCTU cesses, carried out by the Quality Assura team **Sites:** The PI and Research nurse will be GCP trai and familiar with the protocol thereby abl ensure SAEs and SUSARs are reported within timeline stated in the protocol.

Risk/Hazard identified	**Likelihood (Low,Medium or High)**	**Impact (Low, Medium or High)**	**Concerns and Recommendations for m gation and management**
Inadequate monitoring & auditing	**M**	**M**	Monitoring by the LCTU will be undertaken cording to a monitoring plan based on the come of the bespoke risk assessment. It is sumed that on site monitoring will not be quired. This will include GCP, Research Gov ance, and source data checks, as well as m toring of laboratory handling of samples data reliability.
Poor archiving of study related information	**L**	**L**	**LCTU:** LCTU staff will follow the current archiving TM021 when required. **Sites:** Patient data will be managed in accordance local practice, ICH GCP, the Caldecott Guar /National Information Governance Board the Data Protection Act. As part of the LCTU initiation & green light cess, sites will be informed about the archi procedures required for the trial.
Risk/Hazard identified	**Likelihood (Low,Medium or High)**	**Impact (Low, Medium or High)**	**Concerns and Recommendations for m gation and management**

Inadequate patient safety monitoring	**L**	**M**	Sites: As DEFeND is a non-CTIMP trial, surgical com cations and adverse reactions to ARTISS fi sealant will be the only events reported to sess safety. Principal Investigators will re SAEs that are Clavien-Dindo grade IV or abov accordance with the protocol and regulatory quirements. This is delegated to site in the search Site Agreement which is signed prio site opening. As 'surgical complication' is the mary outcome measure of the study, less s ous adverse events will be reported in the sults. LCTU: As part of the study green light, necessary o sight committees must be in place prior to st opening. The Chief Investigator will be required to re all relevant safety information to the relev committees as outlined in the study protoco
Study Design: inadequate study powered recruitment	**L**	**M**	The LCTU has contributed to the design of study. The study has been adopted by the L Trial Adoption Committee and reviewed by NCRI Head & Neck CSG, surgery and local therapies subgroup. Feasibility will be un taken from all identified trial sites prior to set up.

Inadequate costing of the study	**M**	**H**	The study is funded as a doctoral fellowship. costing has been carried out by the LCTU has been scrutinized by the funding body. study is deemed to be low cost so a signifi contingency allowance is not included. The Senior Management Team will regularly view the finances throughout the study
Withdrawal of study funding	**L**	**H**	LCTU Senior management to monitor trial a ity and funding and alert the Sponsor of an sues.
Insurance/indemnity	**L**	**H**	The University of Liverpool will provide non- ligent indemnity.

SECTION 1 Approvals

Chief Investigator signature:		**Date:**	
Sponsor Signature:		**Date:**	
Trial Co-ordinator signature:		**Date:**	

SECTION 2: Intervention Risk Assessment and Safety Monitoring

For safety monitoring, please refer to latest advice from the MRC/DH/MHRA Joint Project on Risk Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Pro ucts.

Intervention risk assessment based on SmPC/Investigator Brochure/protocol/relevant literature

Study Title: DEFeND - Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A rando ised external pilot trial

EudraCT Number: NA

Sponsor(s): University of Liverpool

Intervention Risk Assessment and Safety Monitoring Conducted by: Mandeep Bajwa

Date of Assessment: 16/08/2018

Risk Assessment Version: 1.0

Risks associated with trial IMP(s)/intervention(s) for the IMP(s)/intervention(s) being investigated (single or in combination)

- ☐ CTIMP Type A = Comparable to the risk of standard medical care
- ☐ CTIMP Type B = Somewhat higher than the risk of standard medical care
- ☐ CTIMP Type C = Markedly higher than the risk of standard medical care
- ☒ Non-CTIMP

Justification for type of trial indicated:

The MHRA have deemed DEFeND to be a non-CTIMP. This st is an external pilot of a future phase III trial. Patients undergo neck dissection will either have ARTISS fibrin sealant will be plied to the surgical wound or receive standard of care with ARTISS. Amongst other outcomes, the rate and severity of c plications will be compared. ARTISS fibrin sealant is a comm cially available FDA approved product with a CE mark. It wil used 'on-label' in this study.

Intervention	CTCAE v5 Category	Hazard	Likelihood (L=low; M= Medium; H=High)	Mitigation	Comments
ARTISS Fibrin Sealant	Immune System Disorders	Allergic reaction	L	Exclusion of patients who have a known allergy to Aprotinin Exclusion of patients who have been in contact with fibrin sealant in last 6 months. Exclusion of patients who have allergy to dairy products/bovine protein	ARTISS is administered once during surgery. Any lergic reactions will be noted and treated as a m ter of urgency
	Skin and subcutaneous tissue disorders	Pruritis	L	Nil	This will be treated base on the patients symptom
	Vascular Disorders	Vascular disorders – other Air Embolism	L	Use of spray device in accordance with manufacturer's advice i.e. pressure set to maximum of 1.5 bars and device not held closer than 10cm to wound	
	Injury, poisoning and procedural complications	Seroma	L	Nil	This will be treated base on the patients symptom
	Infections and infestations	Viremia	L	ARTISS fibrin sealant is derived from donated human blood. Standard procedures used to minimise the risk of transmission via blood transfusion are therefore inherent. This includes donor selection and screening of individual donations for specific markers of infection. In addition to this steps have been taken during the manufacturing process to inactivate or remove viruses. The manufacturer states that these measures are ineffective against parvovirus B19. This virus may be serious for pregnant women due to the risk	viruses known to have be transmitted via blood pr ucts in the UK: Hepatitis A, B, C or E Human Immunodeficien Virus (HIV) Parvovirus (B19) Cytomegalovirus (CMV) Human T-Cell Lymphotro Virus (HTLV) types I and

				of foetal infection. Pregnant women have therefore been excluded from the study.	
		Infections and infestations – others Malaria Variant Creutzfeldt-Jakob Disease (vCJD) Any prion disease	L	ARTISS fibrin sealant is derived from donated human blood. Standard procedures used to minimise the risk of transmission via blood transfusion are therefore inherent. This includes donor selection and screening of individual donations for specific markers of infection.	

Pharmacovigilance and processes that have been put in place to mitigate risks to participant safety (IDMC, independent data review,...)

The intervention is considered low risk and investigators will not be required to record AEs. PIs will be required to report SAEs that are classified as Clavien-Dindo grade or above to the sponsor (or delegated other). Reportable SAEs will require immediate reporting by PIs and will allow for monitoring.

The study population are a group of adults who have head and neck cancer and suitable to undergo major surgery. They are likely to have multiple co-morbidities and r have already undergone extensive treatment including radiotherapy and/or chemotherapy.

The process for reporting SAEs listed in the protocol to the sponsor via the LCTU will be defined in the protocol and research site agreement. The LCTU and sponsor will monitor the incidence of reportable SAEs – if this increases during the trial the sponsor (or delegated other) will report this as an unexpected and related SAE to the Research Ethics Committee (REC) within the required timeline. If any SAEs are evaluated as being related to the trial intervention, they will be reported to the REC as an unexpected and related SAE. All SAEs will be reported in the SAE form and a summary provided for the sponsor and the Trial Steering Committee (TSC).

As this is a pilot study, no formal IDMC is required. Instead independent members of the TSC will be responsible for reviewing safety and effectiveness and will provide advice to the TSC and TMG.

SECTION 2 Approvals

Chief Investigator signature:		**Date:**	

Sponsor Signature:		**Date:**	
Trial Co-ordinator:		**Date:**	

SECTION 3: Bespoke Trial Risk Assessment

(participant safety relating to the IMP, study design, methods, safety and rights and reliability of results)

Study Title: DEFeND - Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

EudraCT Number: NA

Sponsor(s): University of Liverpool

Bespoke Trial Risk Assessment Conducted by: Mandeep Bajwa

Date of Assessment: 16/08/2018

Risk Assessment Version: 1.0

1. Intervention

General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Intervention is not standard management practice	Intervention increases risk of known post-operative complications	L	Dose specified in protocol has been chosen according to the appropriate literature and has been peer reviewed by experts within the relevant field Case Report Forms will systematically collect data on patient status	The LCTU will ensure a TSC has been formed for the study as part of the study green light process The LCTU will ensure an interim analysis takes place as planned in the protocol

General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
	Intervention is given to ineligible patients	L	The eCRF does not allow ineligible patients to be randomised.	PI signs off eligibility criteria for all patients before randomisation is permitted. Central monitoring processes to ensure adherence to process.
	Patient is given the wrong treatment	L	Allocation is revealed intra-operatively at the specific time point when ARTISS administration would be required	Theatre staff routinely record batch number of ARTISS administered to the patient. Evidence: • Source data verification • Monitoring visit
Availability or supply of ARTISS fibrin sealant	Patients are given the wrong fibrin sealant	L	Baxter Healthcare LTD will ensure adequate supplies of their product within trial centres	Theatre staff routinely record batch number of ARTISS administered to the patient. Evidence: • Source data verification • Monitoring visit
	Patients are not given the intervention	L	Allocation is revealed intra-operatively at the specific time point when ARTISS administration would be required	Theatre staff routinely record batch number of ARTISS administered to the patient. Evidence: • Source data verification • Monitoring visit
Storage	ARTISS stored inappropriately	L	Reference safety information is provided to site together	No checks required on storage areas by on-site monitoring.

General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			with the product information sheet prior to site activation Information regarding the local facilities will be collected Baxter Healthcare LTD will ensure their product is stored appropriately.	

2. Subject safety, consent, rights and well being

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Breach of Data Protection/confidentiality	Patient identifiable information sent to the trials unit in error	L	Data protection and confidentiality will be covered in the site initiation. All staff in the LCTU complete data protection training to ensure awareness of the regulations. All staff in the LCTU work to the LCTU Data Protection Policy Document. There is no reason for LCTU to receive confidential data as sites will enter anonymised data directly to the study database. The informed consent form contains patient data and copies will be uploaded to LCTU portal as part of monitoring. Consent for this will be requested from participants. Once the consent forms have been checked centrally by two authorised members of LCTU staff they will be permanently deleted from the portal. After this point only the site will	CVs, GCP training and delegation logs are reviewed by senior members of the LCTU as part of the site green light process to ensure that site staff are trained in data protection which should be covered within their GCP training The receipt of any patient identifiable information from site will be recorded and reviewed as part of the central monitoring process. On receipt of any patient identifiers, site will be reminded not to send any unauthorised patient identifiers/re-trained in accordance with LCTU policy. Evidence: • Monitoring plan • LCTU data protection policy • LCTU staff training records • Research site folders/investigator site files • Site initiation presentation • Completed site greenlight checklists

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			have the original signed consent form and there will be no other copies. Sites have the opportunity to have the trial paperwork/procedures reviewed by their Caldicott Guardian prior to giving approval. Patient identifiers have been limited to initials, NHS number and date of birth. NHS numbers can only be used to gain personal information by NHS staff or people with access to the NHS database who will have been trained to follow NHS procedures.	
	Digital data does not have adequate protection	L	MACRO is a web data entry system and has the same security whether the trial is electronic remote data capture or central data management. All data are stored in Microsoft SQL databases on LCTU servers. These servers are located in the	

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			University of Liverpool Computing Services Department. The MACRO system runs on a secure web server which has an SSL security certificate. Data entered on to the MACRO database is encrypted and transferred over a secure web address. Only authorised, trained users are provided with a password to enter data onto the database. Users are given role specific permissions to the correct site and trial.	
Lack of Informed Consent	No consent Patient consented on incorrect version of the PIS and ICF Incorrect information provided to participant	L	PI and RN to have ICH GCP and protocol training highlighting consent process Copy of signed consent form must be received at LCTU before randomisation process can begin LCTU staff to check at randomisation that correct version of PIS	TC to verify ALL trial participants have valid fully informed written consent. TC/DM to record any issue with consent at randomisation into the randomisation audit section of the MACRO database. This audit is reviewed as part of central monitoring.

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			has been provide to the participant. Only REC approved PIS/ICF to be used to consent a patient. If the wrong versions have been used then the correct versions will be provided and the patient re-consented. If the PIS and/or ICF is updated after a patient has been consented then REC will decide if the changes require re-consent. This must follow the study and GCP process for consent and the patient should be informed that they can withdraw if they wish. Re-consent (if required) recorded and tracked through MACRO database. Sites must upload a copy of the new signed ICF to the LCTU portal when patient is re-consented.	Tracking on MACRO will include the versions of PIS and ICF given to patients so that it can be monitored centrally. Copies of the signed delegation log will be kept at the LCTU in the research site files. The electronic trial master file on the portal has an electronic receipt built in to record who has downloaded each document. Evidence: • Original consent forms • Randomisation plan • Electronic receipt of trial documents • Delegation list • CVs & GCP certificates

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			Current REC/HRA approved documents will be managed through the LCTU document management system and made available to site staff via secure LCTU portal. This will include the PIS/ICF. Only REC approved versions of the PIS and ICF will be made available on the PORTAL. The correct version of the protocol and PIS must be stored in the ISF. Copyholders of documents can be accessed via the DMS and can be informed automatically of new versions of documents. Site staff will receive protocol training (as part of SIV) highlighting the consent process for the study. The person taking consent must be named on the site delegation log and be signed off by the PI as suitable for the delegated task.	

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			Site staff should document that informed consent has been taken and that the patient has been entered into the trial in the case notes. The LCTU Document Controller will version control all documents on the PORTAL available to sites.	
Lack of a robust system for the review and expedite reporting of SAEs	SAEs not reported by individual sites. Paper SAEs received by the trial team but not processed. SAEs not reviewed by the clinical co-ordinator and reported to MREC in a timely manner	M	Clear definitions of what constitutes an SAE set out within the protocol along with details of expected events, which would not require reporting. PIs and research nurses made aware of the reporting guidelines and what to report during protocol training. LCTU staff have received pharmacovigilance training and are fully aware of the reporting timelines.	Monitoring and actioning of daily SAE email alerts. Ensuring adequate Clinical Co-ordinator cover for the assessment of SAEs. Senior SAE review rota to monitor the progress of all SAEs reported to the unit to ensure they are processed and reported in accordance with the regulations. Evidence: • Protocol • Pharmacovigilance Plan • CC assessment rota • SAE status reports

Subject safety, rights or wellbeing General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			SAEs to be inputted onto the MACRO pharmacovigilance system as soon as they are received into the unit regardless of whether all required information is present. MACRO pharmacovigilance system set up to send email alerts of SAEs that are incomplete or that have not been assessed by the clinical co-ordinator. Development of a safety Plan for DEFeND will provide guidelines on the correct handling of SAEs	

3. Trial Results

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Slow recruitment - Lack of target population	Overestimation of recruitment target	L	Peer review of study design e.g. by NIHR CSG groups Collaboration with experienced colleagues Early statistical input into study design (LCTU adoption process) Trial Oversight Committees to review and monitor recruitment Recruitment represents a key outcome measure for this pilot/feasibility study. Flexibility to adapt trial design according to barriers Trial progress and recruitment reported at monthly LCTU Business Meetings	Patient Recruitment to be reviewed during Central Monitoring against those rates forecast in the grant application and provided by sites on both the Research Site Agreement (RSA) and Site Specific Information Form (SSI). Evidence: • Central monitoring reports • CSG reports • LCTU Business Management Meeting minutes
Organisational Complexity (Multi-centre sites)	Multi-centre study which can lead to:	L	Site and principle investigator will be selected on their expertise in the surgical management of head and	Central monitoring to be conducted on a monthly basis to identify any issues arising from miscommunication. This will include:

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
	• Inclusion of sites with inadequate trial experience • Necessary approvals not in place • Communication problem		neck cancer as well as their interest and enthusiasm for the trial. All global and local approvals will be checked as being in place as part of the greenlight process prior to recruiting any patients. All teams at sites will have nominated lead nurses to direct communications, support and advice to.	• Protocol compliance • Randomisation compliance • Allocation reveal compliance • Follow-up compliance • Data submission (timelines and quality) • SAE reporting • Recruitment including screening, enrolment and randomisations • Serious breaches 100% source data verification will be conducted for the primary endpoint. Where applicable, central monitoring will be conducted at site level to identify poorly performing centres. Evidence: • Central monitoring reports • Trial site green light checklist • Monitoring plan • Source data verification

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Complexity of trial related procedures	Large number of protocol deviations Serious Breaches Required assessments not completed Randomisation not taking place Allocation not revealed at correct time point during surgery Correct allocation not delivered Drain protocol not adhered to Assessment of trial outcomes not performed by a blinded	M	Site initiation visit for training in study procedures. This will cover enrolment, randomisation, allocation reveal, drain protocol and blinding strategy Confirmation that the site has an appropriate serious breach procedure in place If a serious breach is identified / reported then LCTU's SOP TM037 should be followed Randomisation cannot occur until all important initial assessments are completed in the eCRF. Incomplete data will trigger a data query centrally to prompt the research team as required Randomisation occurs prior to the patient undergoing surgery. Time, date and name of person performing randomisation is logged in the database	Review of protocol deviations and serious breaches Protocol compliance to be reviewed monthly as part of the central monitoring and source data verification report. This will include a review of all protocol deviations and serious breaches Evidence: • Central monitoring reports • Source data verification reports • Monitoring plan

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
	member of the research team		Time, date and name of person revealing allocation is logged in the database Theatre teem to record batch number of ARTISS against the patient in their theatre logbook eCRF has protocol for drain removal in-built. Research team to simply enter drainage volume into CRF after which they will be told to either remove the drain, re-check volume later that day, or leave the drain in-situ Names of surgical team in theatre during the allocation reveal will be recorded. The database will forbid these individuals from assessing &/or entering data thereafter.	
eCRF data	eCRF not fit for purpose e.g. CRF does not collect tumour lesion at baseline	M	LCTU eCRFs are designed and validated in-house. The database used has password access, audit trail and back up.	Central monitoring to be conducted monthly which will include a review of the number and type of data queries raised across all sites

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
	Inaccurate data collected Incorrect data entered		CRFs will be reviewed by the trial statistician, co-investigators in the relevant fields, the chief investigator and some site research nurses prior to implementation. Data Query Process Plan to be implemented to ensure discrepancies are queried in a standardised manor with easy to understand questions and comments. A data management plan will be put in place to ensure consistency across data entry personal and clear guidelines on timelines for data entry. Early entry of data will allow problems with completion to be identified and addressed as early as possible preventing ongoing problems in future patients. MACRO will include validation rules to alert the user to inconsistent data that is inputted. All data are backed up every night	and monitor and completeness rate across sites Central monitoring will allow specific problems with the CRF to be identified and addressed Independent members of the TSC will review the data completeness quality 6 monthly. Study will be subject to the LCTU data entry QC check process. Evidence: • Independent member TSC report • Data management plan • Data query process plan • ECRFs • Monitoring plan • Central monitoring reports

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			in several secure locations.	
Lack of provisions for efficacy and safety analyses	No unbinding procedure. Unintentional unblinding by surgical team who are not blinded. No formal pre-specified analyses.	M	It is unlikely that this trial will require unblinding as the ARTISS is administered only once in the theatre environment. The surgeon applying the ARTISS will not be blinded. The patient, surgeons assessing outcomes, ward nurses and research nurses will be blinded. The main clinical endpoints of interest (Clavien-Dindo, removal of drain, fitness for discharge) require the assessment of a surgeon. Therefore operating surgeons (who are unblinded) need to delegate these assessments to suitable blinded colleagues. A severe hypersensitivity reaction, air embolism or transmission of an infective agent constitute a serious adverse event and may be attributable to the administration of ARTISS. If they occur, severe hypersensitivity and air embolism would be anticipated to occur during or immediately after administration in the	Independent members of the TSC to review unblinded safety and efficacy data on a 6 monthly basis. All patients who have been unblinded will continue to be followed up as per the schedule set out in the protocol to ensure patients are not being unblinded unnecessarily. This data will be reviewed through central monitoring and by the independent members of the TSC. Evidence: • TSC report plan • Central Monitoring Reports • Statistical Analysis Plan • Data worksheet

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			theatre setting. Staff caring for the patient at this time will not be blinded so there will not be a delay in diagnosis and emergency management. If they did happened, the patient, outcome assessors and nursing staff would be unblinded only if the information is required for the ongoing medical management of the condition. In the event that the patient is diagnosed with an infectious disease that was not diagnosed pre-operatively, they will be unblinded. Based on the 'Serious Hazards of Transfusion' 2016 annual report, the following infectious diseases are known to have been transmitted via blood products in the UK: 1. Hepatitis A, B, C or E 2. Human Immunodeficiency Virus (HIV) 3. Parvovirus (B19) 4. Cytomegalovirus (CMV) 5. Human T-cell Lymphotropic Virus (HTLV) types I and II	

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			6. Malaria 7. Variant Creutzfeldt-Jakob Disease (vCJD) or any other prion disease If the patient is newly diagnosed with any of the above infectious diseases, they will be unblinded and immediately referred to the appropriate medical specialists for treatment. The surgeon will be unblinded to the surgical procedure performed and is required by the protocol to maintain the blind. The surgeon must not state whether ARTISS was used in the patient's notes or on the CRF. Surgeons are requested to state that the wound closure conducted in accordance with the DE-FeND trial randomisation in the patient's notes as per protocol. A statistical analysis plan will be produced within 3 months of the study greenlight checklist being complete which will detail the formal	

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			procedures to be undertook when analysing the results of the trial.	
Relevant data missing	CRF does not collect important baseline data Follow-up is too infrequent to capture key data items Poorly design case report form No procedures in place to ensure a timely flow of data from sites Site non adherence to the protocol No database backup plan	L	CRF design undertaken with study chief investigator and trial statistician The issue of timely CRF completion and return to the LCTU will be addressed in the protocol training sessions along with the importance of Data Query Process Plan to be implemented to ensure discrepancies are queried in a standardised manor with easy to understand questions and comments. A data management plan will be put in place to ensure consistency across data entry personal and clear guidelines on timelines for data entry. Early entry of data will allow problems with completion to be identified and addressed as early as possible preventing ongoing problems in future patients.	Central monitoring to be conducted on a monthly basis and will include a review of all protocol deviations, data queries and data retrieval rates across sites. Central review will allow specific problems with the CRF to be identified and addressed. This will be reviewed by the TMG periodically. Independent members of TSC to review of the data completeness quality and photograph compliance at the end of the pilot phase and at least yearly thereafter. Evidence: • TSC Report Plan • Data management Plan • Data Query Process Plan • CRFs

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			LCTU CRFs, the MACRO trial database and associated systems are designed and validated in-house. All databases are access controlled by the Information Systems department. All data are backed up every night in several secure locations.	• MACRO validation documents • Monitoring plan • Central monitoring reports • TMG meeting minutes
Poor quality data	Un-validated database No audit trail Fraudulent data	L	MACRO database will undergo a full program of validation in accordance with LCTU standard operating procedures prior to going live for trial data. MACRO is designed specifically for clinical trials and has a full audit trail and appropriate validations. Site personnel GCP trained and reminded during protocol training of the importance of accurate	Monthly central monitoring reports will look at key data metrics including: • Data query rates • Missing data Ongoing quality assurance checks on data entry including 100% check of all primary endpoint data and 10% of everything else.

Trial Results General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			CRF completion and maintaining accurate and well organised source documents.	
Inadequate medical record keeping (e.g. archiving)	Unable to reconstruct the trial. Missing documents at site closeout.	L	Study archiving to be done in accordance with LCTU SOPs. Research Site Agreement to specify timelines for archiving data relating to the study. Site personnel alerted to new documentation as and when it becomes available throughout the course of the study and training will include use of the portal and the document repository.	Study close out to be completed in accordance with LCTU SOP, including a check of all essential trial documents before sponsor permission to archive is given.

4. Facilities, Equipment and Resources

Facilities, equipment and recources General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Insufficient Investigator facilities/resource	Inability to perform the randomisation via the web based tool	L	Research Site Agreement must be signed off by all parties prior to site green light	Evidence: • Greenlight checklist • Research site agreement

Facilities, equipment and recources General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
	No facilities to process and store translational microbiology samples No facilities to store ARTISS fibrin sealant		Site initiation visit to ensure site has a freezer that can store translational samples at -80C Baxter Healthcare LTD to review site facilities to ensure site has the appropriate facilities to store ARTISS	
Inexperienced Clinical team	Personnel other than the PI and pharmacist have never been involved in a clinical trial Incorrect advice to patients about surgical intervention	M	LCTU to obtain current CVs and GCP training records to assess suitability of staff qualifications, training and experience prior to site opening LCTU provide a template delegation log for PI to formally authorise delegation of tasks to appropriate site personnel Site research staff trained on the use of ARTISS and the trial procedures at the site initiation visit Only PIs/sites with experience of head and neck surgery will be selected to participate	CVs, GCP training and delegation logs are reviewed by senior members of the LCTU as part of the site green light process TC to carryout site research site specific training at initiation presentation Independent oversight of safety reporting by independent members of the TSC

Facilities, equipment and recources General Risk Identified	Potential Risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
			Site staff delegation log with clearly defined delegation of responsibility ensures site research staff are aware of their responsibilities	

5. Documentation, Governance and GCP Compliance

Documentation, Governance and GCP compliance General Risk Identified	Potential risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Trial Master File (TMF)	Lack of documentation to reconstruct trial and confirm compliance with CT regulations, the protection of subject's rights/well being/safety and the reliability of the trial results.	L	LCTU SOPs are in place to cover the maintenance of the trial master file and these must be followed by the LCTU trial team The research site agreements state that all site and patient documentation must be kept by the participating site An electronic TMF is maintained on the LCTU portal for access by Sponsor and participating sites	The electronic TMF on the portal has an electronic receipt built in to record who has downloaded each document and when.

Documentation, Governance and GCP compliance General Risk Identified	Potential risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Inadequate Monitoring	Non-compliance with regulations Lack of source data Data reliability	L	Trial Oversight Committees must be in place and is checked as part of the LCTU study green light checklist LCTU monitoring plan template must be customised for the study and based on this risk assessment. The monitoring plan must be in place prior to study opening and this is checked as part of the LCTU study green light checklist	LCTU green light process; green light checklist must be signed by LCTU senior management prior to study opening.
Insufficient Sponsor Overview of study	LCTU are carrying out duties which are not formally delegated such as SUSAR reporting/serious breaches/urgent safety measures Sponsor are unaware of protocol amendments	L	Responsibilities clearly documented in the appropriate agreements and in the Sponsor communication plan Provide Sponsor with access to LCTU portal (study documentation and safety data) All study amendments must be reviewed by the Sponsor using the Sponsor Assessment Form in accordance with LCTU SOPs and Sponsor communication plan	Internal audit of LCTU processes carried out by the Quality Assurance team Regular reporting to the Joint Research Office sponsorship committee

Documentation, Governance and GCP compliance General Risk Identified	Potential risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
Lack of qualifications or training in research team to carry out assigned duties	Data Manager has not received training on MACRO databases before entering study data Research team member has not received ICH GCP, data protection training	L	LCTU induction training programme is arranged for new members of staff as required Regular ICH GCP training is arranged for LCTU staff Trial Co-ordinator to ensure training is documented on the LCTU web portal and the LCTU delegation log	Internal audit of LCTU processes carried out by the Quality Assurance team
Long term absence or vacancy of research team member post	Trial Co-ordinator absent on long-term sickness leave	L	Each tumour group has a designated tumour group lead who has sufficient study knowledge to cover the Trial Co-ordinator's key duties	Regular Trial Co-ordinator and business management meetings to review resources
Lack of adequate LCTU SOPs or plans	No process documented for pharmacovigilance/randomisation or registration procedures Overall Trial Greenlight process not followed	L	Clear LCTU SOPs/plans describing trial procedures must in place as part of the LCTU study green light checklist	LCTU study green light checklist must be signed by LCTU senior management prior to study opening Internal audit of LCTU processes carried out by the Quality Assurance team
Lack of QC and QA systems implemented and maintained	MACRO database not validated prior to entry of patient data	L	Database validations must be completed as part of the LCTU study green light in accordance with the timelines stated in the relevant SOPs	LCTU study green light checklist must be reviewed by LCTU senior management within the timelines specified in the relevant SOPs

Documentation, Governance and GCP compliance General Risk Identified	Potential risks	Likelihood (Low, Medium or High)	Mitigation or Adaption	Monitoring methods to address
SECTION 3 Approvals:				
Chief Investigator signature:		**Date:**		
Sponsor Signature:		**Date:**		
Trial Statistician:		**Date:**		
Trial Co-ordinator:		**Date:**		

A.6 Internal Delegation Plan

This Internal Delegation Plan establishes a set of guidelines for the tasks and responsibilities relating to the delivery of the DEFeND study.

The purpose of the plan is to identify the processes and activities that will take place across different departments within the University of Liverpool in relation to the trial and will be used to document the roles and responsibilities of study personnel and key stakeholders. The plan establishes and formalises how all aspects of the trial will be managed and how the sponsor will ensure oversight of study activities. The plan is a living document and may be reviewed and updated as required.

1. ABBREVIATIONS:

CTU	Clinical Trials Unit. For this trial this is Liverpool Cancer Trials Unit
CI	Chief Investigator
RSO	Research Support Office
UoL	University of Liverpool
PIS	Patient Information Sheet (PIS)
ICF	Informed Consent Form
REC	Research Ethics Committee
GCLP	Good Clinical Laboratory Practice
HRA	Health Research Authority
DSUR	Development Safety Update Report
QC	Quality Control
QA	Quality Assurance

2. INTRODUCTION:

The University of Liverpool (UoL) have agreed to take on sole sponsorship for the DEFeND trial.

The trial is being led by the Chief Investigator (CI) Mr Andrew Schache and will be managed through the LCTU. The recruitment and treatment of trial participants will take place in 2 NHS sites (Aintree University Hospital and Queen Victoria Hospital) and each will be subject to a formal agreement.

The trial is funded by the NIHR as a Doctoral Research Fellowship.

3. TRIAL DETAILS

Trial Title:	Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial
ISRCTN Number:	99181100
Sponsor:	University of Liverpool
Sponsor Code:	UoL001346
IRAS Reference:	234851
REC Ref:	NW/18/0209
Chief Investigator	Andrew Schache
Patient Population	Patients with Head and Neck Cancer due to undergo Neck Dissection Surgery
Sample Size:	50
Objectives:	Pilot/feasibility endpoints
Planned Duration:	12 months
Funder:	NIHR
Number of Research Sites:	2 (Aintree University Hospital & Queen Victoria Hospital)

4. GOVERNANCE and STANDARDS

The UoL will undertake the role of Sponsor in line with the current regulations applicable to this research including, but not limited to the Medical Devices Regulations 2002, UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017), the EU General Data Protection Regulation 2016 and Data Protection Act 2018, Human Tissue Act 2004, Mental Capacity Act 2004 and Good clinical practice guidance

The Trial will convene a Trial Steering Committee (TSC). As this study is an external pilot trial, an Independent Data Safety Monitoring Committee (IDSMC) will not be convened, rather the TSC will have independent members who will take on this extended role.

All study specific activities, analyses and procedures will be undertaken according to the DEFeND Trial Protocol which is approved by the Chief Investigator, Liverpool Joint Research Office Sponsorship Committee, trial statistician and the CTU Director.

5. CONTRACTS and FINANCIAL MANAGEMENT

The University Legal and Compliance Office will be responsible for drafting and negotiating contracts with external parties required for the trial. The (Deputy) Operational Director of LCTU is be delegated the function

of signing non-modified Research Site Agreements, otherwise the Legal and Compliance Office will also be responsible for preparing and signing off contracts and will provide copies of all agreements to the CTU for inclusion in the Trial Master File. Prior to providing the green light to proceed, the CTU will check all appropriate contracts are in place.

The University Research Support Office (RSO) will deal with the financial aspects of the trial including invoicing and payments. The PhD student will be responsible for reporting to the funder in line with the terms and conditions of the funding award.

6. INSURANCE and INDEMNITY

The University of Liverpool is responsible for ensuring that there is adequate insurance in place for the conduct of the DEFeND trial.

7. PROTOCOL and SUPPORTING DOCUMENTS

The protocol has been written by the CI and has received Sponsor approval from the University of Liverpool. Peer review of this trial was conducted by the NIHR. Prior to trial initiation the CTU will conduct SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Quality Assurance checks on the Protocol to ensure all the key requirements have been included, unless the LCTU Protocol template has been used.

The Patient Information Sheet (PIS), Informed Consent Form (ICF) and all other participant documentation will be prepared by the CTU in accordance with their current SOPS and in accordance with current HRA guidance.

The CTU will maintain approvals and the version control of all trial related documents and make approved documents available via the LCTU online web portal to the research site and the Sponsor.

All trial related documentation will be submitted to and approved by an Independent Ethics Committee prior to trial start.

8. REGULATORY and ETHICAL SUBMISSIONS

The following approvals will be required for the global conduct of the trial:

- Ethical approval by a REC within the UK Health Departments' Research Ethics Service
- HRA Approval for assessment of governance and legal compliance (for research where the lead NHS R&D Department is in England)

The regulatory and ethical submissions will be conducted by staff within the CTU in collaboration with the Chief Investigator. The CI and RSO will review and approve the content of all applications prior to submission.

HRA Approval is the process for gaining NHS permission in England that brings together the assessment of governance and legal compliance and is undertaken by dedicated HRA staff. It replaces the need for local R&D checks of legal compliance and related matters by each participating organisation in England. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study.

The provision of NHS Capacity and Capability (for English sites) / R&D permission (for devolved nation sites) will be delegated to NHS organisations via the Research Site Agreement. The CTU will confirm this permission is in place prior to site activation.

An Annual Progress Report will be produced by the CTU in line with HRA guidance and submitted on anniversary of the ethical approval until trial closure.

9. AMENDMENTS

The CI and the CTU will prepare all amendments for review and provide all the required documentation to the RSO.

The Chair of the JRO Sponsorship Committee will review and approve all amendments on behalf of the Sponsor and make the decision regarding substantiality. This decision will be communicated to the Trial Coordinator by the Clinical Research Governance Team within the RSO.

Post review the CTU will manage the submission of amendments to the ethics committee, MHRA and NHS site as indicated. The CTU will ensure all Principal Investigators (PIs) are aware of amendment and will ensure approvals are in place prior to implementation.

10. RESEARCH SITE CONDUCT

The trial will be conducted at 2 centres within the UK (Aintree University Hospital & Queen Victoria Hospital).

All duties and responsibilities relating to the conduct of the trial at the site will be delegated via a research site agreement. The agreement will be drafted using the model Agreement for Non-Commercial Research in the Health Service[1] and will delegate the following responsibilities:

a) Ensure that legislation in relation to research is followed within the Site
b) Ensure that the Trial Site team members are appropriately qualified and experienced to undertake the conduct of the Trial and that they have current substantive or honorary employment contracts in place.
c) Ensure that no Participant is recruited until a favourable ethical opinion and no objection for use of the device has been provided
d) Put and keep in place arrangements to allow all to conduct the Trial in accordance with the Protocol

[1] http://www.ukcrc.org/regulation-governance/model-agreements/mnca/

e) Ensure that the rights of individual Participants are protected and that they receive appropriate medical care whilst participating in the Trial.
f) Maintain and archive Trial documentation at the Site
g) Ensure that all data and documentation are available for the purposes of monitoring, inspection or audit and that the appropriate consent has been provided by the Participant
h) Ensure adequate facilities, resources and support are available to conduct the Trial at the Site
i) Inform appropriate health or social care professionals if their patient is a Participant in the Trial in accordance with the UK Policy Framework.
j) Report suspected research misconduct at site to the sponsor
k) Maintain detailed records of all adverse events occurring in trial participants and report events in accordance with the protocol to the sponsor
l) Ensure that the site completion, provision and maintenance of; Source data, subject identification log, Case Report Forms, data queries, adverse events and clinical trial documentation.
m) Ensure that all laptops and external storage devices used for trial data are encrypted
n) Ensure that samples are collected, and managed as agreed in the Protocol and Sample SOPs

Each research site will be monitored by the CTU. This process is described in section 13.

Prior to the initiation of the trial, the HRA Approved Statement of Activities, Schedule of Events and supporting documentation will be submitted to the Research and Development Department for Confirmation of Capacity and Capability approval in accordance with local NHS Trust procedures. Evidence of Site Confirmation of Capacity and Capability will be checked prior to site activation by the LCTU.

11. SAFETY REPORTING

The CTU will manage the safety reporting for the trial in accordance with the CTU Pharmacovigilance SOP (TM031 – Pharmacovigilance and Safety Reporting). The CTU will maintain detailed records of all adverse events as specified in the protocol. The trial will have a trial specific safety plan in place prior to trial green light which will document in detail the different elements of safety reporting for the specific trial. The CTU will prepare and submit all safety reports that are deemed as requiring expedite reporting to the MHRA and the Ethics Committee on behalf of the sponsor. Furthermore, the LCTU will ensure all the investigators are in possession of all the current safety information relating to the trial.

The LCTU will provide line listings of all Serious Adverse Events reported on the trial to the RSO every 6 months. If any concerns are raised following department review of this report it may be escalated to the Joint Research Office Sponsorship Committee. The TSC will meet 6 monthly to review the progress and safety of the trial in accordance with the TSC charter and associated report Plan.

12. DATA MANAGEMENT and CASE REPORT FORMS

The CTU with Collaboration with the Chief Investigator design the Electronic Case Report form for the trial and build the corresponding database. The eCRFs for this trial will be developed using MACRO software. The

research sites will enter all patient data directly into the eCRF on MACRO. There will be no paper CRF. Sites will however be provided with a workbook for all clinical entries which will be considered a source document. The purpose of this document is not a substitute CRF, rather to simplify the source data verification process.

The trial MACRO databases will automatically be added to the LCTU Quality Control (QC) system. This system identifies all data that are linked to Primary Outcomes and all safety data. All other data are subjected to a random 10% QC check. QC is carried out by LCTU data managers as part of their daily tasks (SOP DM006 Quality Control (QC) of Trial Databases).

Data Queries will be raised on any data items that are missing or have a warning triggered. These queries are raised by the Data Manager and are automatically sent to the data collection contact at the research site for resolution (SOP DM003 For Designing a Data Query Process Plan and trial specific Data Management Plan).

All data on all LCTU servers are controlled, stored and backed up in accordance with GCP regulatory requirements. Access to data is strictly controlled by the LCTU IS department via user access forms (SOP IS009 User Access Control). Servers are located in a secure server room with appropriate environmental controls (SOP IS005 Computer Systems Security Maintenance and Environmental Control).

Each computer system will be fully validated and tested prior to being used for the trial in accordance with LCTU SOPs IS006 MACRO Database Design and Validation and IS003 Development and Testing of Non-MACRO Systems.

13. RISK ASSESSMENT and MONITORING

The CTU will perform a risk assessment as per SOP TM005 – Risk Assessment to evaluate the risks of all aspects of the trial and determine suitable mitigation and monitoring strategies to balance the risks identified. This will then be transcribed in to a trial monitoring plan in accordance with the CTU SOP TM025 – Clinical Trial Monitoring.

The trial will be monitored by the CTU in accordance with the bespoke trial monitoring plan and will be monitored by a mixture of on-site, triggered and central monitoring strategies. Central monitoring reports will be discussed at each Trial Management Group and copies will be provided to the RSO in line with the TMG meetings. A bi-annual compliance report will be provided to the RSO and the findings presented to the Joint Research Office Sponsorship Committee to allow oversight of research site conduct and trial delivery. If any issues are identified at any time other than specified above the CTU will report these to the RSO who may then report to the Joint Research Office Sponsorship Committee.

14. LABORATORY ASPECTS

The duties, procedures, processes and analyses relating to microbiology wound and oral cavity swabs collected as part of the clinical trial will be performed in accordance with the University of Liverpool Institute of Infection and Global Health Research Laboratories SOP.

The University of Liverpool Institute of Infection and Global Health Laboratories will be responsible for the production of sample collection kits and quality control.

The DEFeND Trial Sample Collection Kits (each with their own unique kit identification code) are prepared to contain all components to collect samples from patients, with documentation. All kits sent out to the sites to obtain patients samples for the Trial will be prepared according a kit building SOP.

All samples received into the Research Laboratory will be done so in concurrence with the Research Site Agreement (RSA) between the trial sponsor and each participating site providing samples. The samples to be collected are outlined below.

Swab Site	Intra-operatively	In-patient Post-operatively	Follow-up 1	Follow-up 2
Oral Cavity	X	X (each day)	X	X
Cutaneous Neck Wound	X	X	X	X

Samples will be stored by the University of Liverpool Institute of Infection and Global Health for a minimum of 15 years.

15. QUALITY ASSURANCE

The CTU will be responsible for Quality Assurance (QA) of the trial management activities and the Liverpool GCLP facility will be responsible for the QA relating to the laboratory activities. The University will retain Sponsor oversight of the LCTU and the trial, either of which may be subject to audit either as part of the annual audit plan, or as a triggered audit.

16. TRIAL MASTER FILE

The CTU will be responsible for the maintenance of the Trial Master File (TMF) and will make this available for Audit/Inspection as required.

17. ANALYSIS of DATA

The CTU will be responsible for the analysis of data.

18. SERIOUS BREACHES/MISCONDUCT

It will be the responsibility of all parties involved in the trial to report any suspected misconduct or serious breach to the RSO for assessment.

In cases were a serious event occurs that does not fulfil the criteria of a serious breach, SUSAR or other event reportable in line with the Regulations and reporting requirements the CTU should discuss this event with the Sponsor to evaluate and confirm any further action. Such cases may be where reputational or financial harm to the organisation may occur

19. BLINDING

Blinding will be performed and maintained by the CTU. The process of unblinding treatment will be documented in the DEFeND Unblinding Plan.

Function/responsibility	University responsible department	Lead contact Person	SOP and or Documents (if applicable)	NOTES
Contract for the supplies required for the trial	Legal and Compliance	Head of Research Contracts	RSO SOP016 Production and Management of Contracts for University Sponsored Clinical Research Activity	
Ensure that the insurance/indemnity arrangements are in place to cover liabilities	Legal and Compliance	Insurance Manager	RSO SOP004 Sponsorship Application and Approval Process	
Invoicing and Payments	Research Support Office		N/A	
Protocol writing and Scientific Review	Department of Molecular and Clinical Cancer Medicine Research Support Office	CI Research Integrity and Governance Manager	LCTU SOP TM001 Protocol Development and content for clinical trials involving medicines for human use. LCTU Template TM001_TEMP1 LCTU Protocol Template	CTU to complete a SPIRIT checklist review prior to submission to ethics, unless the LCTU Protocol template has been used. Peer review completed as part of funding application and CTU trial adoption. JRO Sponsorship Committee have reviewed the scientific peer review and protocol
Preparation of PIS and ICF	Clinical Trials Unit		LCTU SOP TM002 Creating a Patient Information Sheet and Informed Consent Form	To be reviewed by patient group prior to submission to ethics

Design of Case Report Forms and database	Clinical Trials Unit		LCTU SOP TM011 Case Report Form Development and Design LCTU TM011_TEMP1 CRF Portrait Forms LCTU TM011_TEMP2 CRF Landscape Forms	
Document Control and Trial Master File	Clinical Trials Unit		SOP TM15 Creating and Maintaining a Trial Master File SOP GE007 Version control and distribution of documents through the LCTU DMS	
Ethics Application	Clinical Trials Unit		LCTU SOP TM006 For obtaining HRA Approval Ethical Approval Letter HRA Approval letter	
Registration of trial with a publically accessible database	Clinical Trials Unit		LCTU SOP TM027 Public Registration of a Clinical Trial	
Obtain NHS Confirmation of Capacity and Capability	Research Sites and Clinical Trials Unit	N/A	LCTU SOP TM043 Trial Site Green Light Process	To be delegated to NHS Organisation through a research site agreement.

			NHS Confirmation of Capacity and Capability	The CTU will check NHS permission for each site prior to drug release at a site in accordance LCTU SOP TM043
Amendments and urgent safety measures	Clinical Trials Unit and RSO		LCTU SOP TM009: Making Substantial and Non-Substantial Amendments RSO SOP SOP018 Procedure for the Submission of Amendments and Taking Urgent Safety Measures	RSO to make the decision regarding substantiality and LCTU will process the amendment. This will include submission to Ethics, HRA, MHRA and recruiting sites (where applicable) The LCTU will ensure that the research site has all the required documentations and is aware of any amendment
Monitoring	Clinical Trials Unit		LCTU SOP TM005 Risk Assessment Risk Assessment (**RADEF001 – DEFeND Risk Assessment**) LCTU SOP TM025: Clinical Trial Monitoring Trial Monitoring Plan	
Safety Reporting and maintenance of detailed records of all adverse	Clinical Trials Unit		LCTU SOP TM031: Pharmacovigilance and Safety Reporting	

events as specified in the protocol			Trial Specific Safety Plan **(SSDEF_D009 – DEFeND Safety Plan)** TSC Charter **(SSDEF_D012 – DEFeND TSC Charter)**	
Data management and Information Systems	Clinical Trials Unit		LCTU SOP IS006 MACRO Database Design and Validation LCTU SOP IS003.4 Development and Testing of Non-MACRO Systems LCTU SOP DM006 Quality Control (QC) of Trial Databases LCTU SOP DM002 Procedure for CRF Tracking LCTU SOP DM003 Designing a Data Query Process Plan LCTU SOP DM005 Designing a Data Management Plan	
Annual Reporting to REC	Clinical Trials Unit		LCTU SOP TM010 Annual Ethical Progress Report	
Serious Breaches/Misconduct	All		LCTU SOP TM037 Identification and	

			Notification of Serious Breaches of GCP or Trial Protocols LCTU Template TM_D012 Serious Breach of GCP or the Trial Protocol Assessment and Notification Form	
End of Trial Notification	Clinical Trials Unit		LCTU SOP TM020 Closing a Trial	
Analysis of data	Clinical Trials Unit		LCTU SOP IS012 Producing Data Snapshots for Analysis LCTU SOP ST001 Statistical Analysis and Reporting LCTU Template ISDMC Statistical Analysis Reporting LCTU Template ST001_TEMP2 Final Statistical Analysis Reporting	
Initiate and coordinate review and submission of abstracts, posters and publications	Clinical Trials Unit		N/A	

Archiving of essential trial documentation and TMF	Clinical Trials Unit		LCTU SOP TM021 LCTU Archiving Procedure LCTU SOP IS013 Study Closedown and Archiving LCTU Template TM021_TEMP1 Archiving Consent Form LCTU Template TM021_TEMP2 Destruction of Archived Materials Consent Form LCTU Template TM021_TEMP3 Archive Box Label LCTU Checklist TM021_CHK1 Archiving Quality Control Form APTLOG_D017 Archive Log	
INSERT FURTHER TRIAL SPECIFIC RESPONSIBILITIES				

This Plan will be reviewed at such a time where significant change is made to the trial or University personnel.

Sponsor University of Liverpool Print Name: LARA LAVELLE-LANGHAM	Signature: D. Lavelle-Langham Date: 18/10/18
CI Print Name: ANDREW SCHACHE	Signature: Date: 31.10.2018.
Director Clinical Trials Unit Print Name: PIAVA GHAVAEE	Signature: Date: 2/11/18.
INSERT OTHER SIGNATORIES AS REQUIRED – E.G. GCLP LAB	

A.7 Data Management Plan

DEFeND

Data Management Plan for DEFeND Trial

Version Number: 1.0
Dated: 16/08/2018

Author: M. BAJWA Signature: [signature] Date: 26/09/2018

Reviewer: R. HANSON Signature: [signature] Date: 26/08/2018
(TC)

Authoriser: A. SCHACHE Signature: [signature] Date: 19.9.2018
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ISRCTN Number 99181100

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1. Introduction

This Data Management Plan (DMP) is in place to help guide the conduct of the DEFeND trial. This plan details the data management process for DEFeND, and aims to ensure that the data are of the highest quality, that there is conformity across trial teams, and demonstrates that there are robust systems to provide quality checks and validation.
Specifically the plan will identify:

- What processes are performed
- Who is responsible for the processes
- How the processes are performed
- Who will perform them
- What documentation needs to be produced or collected

The plan will encompass all elements of the data management process for the DEFeND trial.
This DMP is a working document and should be updated throughout the course of the trial if amendments are necessary. The DMP will be reviewed annually by the DEFeND Trial Coordinator (TC), who has responsibility for this review and any updates to the DMP.
Amendments to the DMP will be processed by the Document Controller to ensure accurate version control, archiving and the distribution of current documents. The actions of this document will comply with GCP and the EU Directive 95/46/EC, specifically Articles 16 & 17.

2. Trial Background

This study is designed as a multicentre randomised external pilot trial with two arms. Patients due to undergo neck dissection surgery for head and neck cancer will be randomised to either the interventional arm or the control arm on a 1:1 basis. Patients will be stratified according to site (hospital) only. The 2 UK centres recruiting to the study are Aintree University Hospital and the Queen Victoria Hospital. In the interventional arm patients will undergo a neck dissection and have Artiss fibrin sealant (Baxter Healthcare LTD) applied as part of wound closure. In the control arm patients will simply undergo a neck dissection and have their wound closed without Artiss (standard of care). The allocation will be revealed at a specific time point during surgery (point of wound closure). Both the patient and outcome assessors will be blinded to the allocation. The patient will be followed up for a period of 6 weeks post-operatively before exiting the study.

(See current version of protocol for more detailed information)

3. Data Sources

ICH E6 defines a Case Report Form (CRF) as 'A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject'. A CRF is a source document and is classified as a complete form whether it is one page or several pages.

All source documents will remain at site. No source documents will be stored at the Liverpool Cancer Trials Unit. All other trial related documents are stored under secure conditions. The Cancer Research UK Liverpool Cancer Trials Unit (LCTU) is housed in a building that is secured by swipe card access for authorised personnel and documents are kept in locked cabinets. The office is locked when not attended.

4. Hardware and Software used for data handling.

Once data have been collected it will be entered into an electronic database. This database was designed and setup using a software program called MACRO.

MACRO is specifically designed for creating a custom-built trial database. It allows clinical trial data to be collected, validated and stored securely. The main reasons for choosing MACRO are given below:

a) Quick CRF design.
Past trials involved employing a computer programmer to design and setup the electronic data capture forms, a lengthy and inefficient process. MACRO has a built in CRF designer which allows the designer/programmer to quickly and easily convert paper CRFs into online CRFs.

b) Price.
MACRO represents better value for money than other clinical trial software. Its significantly lower cost means resources can be directed elsewhere in the LCTU.

c) Fully GCP and EU Directive compliant.
As MACRO is designed solely for the use in clinical trials it is fully compliant with all GCP and EU directives, including full audit control and tracking of data changes. All user activity is logged and cannot be deleted or edited.

d) Good Reputation.
Other clinical trials units currently using MACRO (including London and Leeds) gave good reports on the efficiency and general use of MACRO.

MACRO contains three main data collection components; the Microsoft SQL database used to store the raw data, the client-side software programs, and the web-based application for data entry. The LCTU currently runs version 4 of MACRO. It consists of a MS SQL database (Microsoft SQL Server 2008) that sits on a secure University server (LCTUDATA). This server is backed up. The web and server components for MACRO 4 run on a separate University server (LCTUWEB).

The web front-end allows data entry remotely, and can be accessed from any computer with an internet connection. The MACRO data entry page uses an SSL (Secure Sockets Layer) certificate to ensure that all data sent to and from the server are kept secure.

Any urgent hotfixes or updates released by Infermed (the developers of MACRO) are implemented. Any major upgrades or new releases are tested on one of the testing servers before the live server is updated *(See SOP IS006 MARO Database Design and Validation)*

Updates to records such as lists of PIs, hospitals and surgeons are made on an ongoing basis as sites are added to the trial. Updated records will be provided by the TC and sent to the Database Developer (DD) who can implement them without the need for further approval.

5. Other related Standard Operating Procedures (SOPs) & documents.

95/46/EC Data Protection Directive
The Data Protection Act 1998.
IS012_TEMP1: Data Extract Request Form
INS_D008: MACRO 4 User Guide
SSDEF_D009: DEFeND Safety Plan
SSDEF_D011: DEFeND Randomisation Instructions
SSDEF_D016: DEFeND Data Query Plan

For other non-trial specific related SOPs, please refer to *SOP DM005 Designing a Data Management Plan, Section 4*

6. Data Handling Plan

Data handling includes the collection, collation, counting, grouping, randomising, recording, source data verification (where Trial Monitor(TM) is in use), transportation, security, storage and entry of patient data from source documentation (CRFs).

6.1 eCRF Completion, Receipt and Storage

eCRF completion via MACRO v4 database is the required method of data collection. Delegated staff who have their current CV (signed and dated) and GCP (dated in the last 3 years) will be given access to login.

For instructions:

- Randomising a patient, please refer to the DEFeND Randomisation Instructions
- Data entry and eCRF completion, please refer to the DEFeND eCRF Completion Guidelines
- SAE reporting, please refer to the DEFeND Safety Plan

Site staff are expected to input data directly into the eCRF via MACRO v4 in real time. The delegated person will have a unique username and password to identify who entered the data for audit trail and training purposes. Sites are expected upload data in real time i.e. each day of the patient's inpatient stay and at each clinic visit. The DM will have 1 week to review the data and raise any necessary queries. Site will have 1 week to respond to the queries, the DM then has 1 week to review responses and either close the query or ask for further information (**3 weeks in total**). Both sites and DM will be notified by automatic email that there is data/queries to review in MACRO. Sites may be visited by the TC in accordance with the trial specific monitoring plan. Sites will be contacted as required by the TC to discuss any training issues that may arise.

Consent Forms

The DEFeND trial uses central monitoring and requires consent forms to be uploaded to the LCTU portal with the patient's identifiable data still visible. The consent forms will be checked by two independent members of the central trial team. Once these checks have taken place and the consent considered valid, the uploaded document will be permanently deleted. Any further reference to the consent will need to be performed by accessing the original hard copy stored at site in the patient's medical records.

Patient Reported Questionnaires

Electronic versions of the patient reported questionnaires will be stored on the LCTU Portal. It is expected that sites will download the questionnaires and hand them to patients for completion at specific time points as stipulated in the protocol. It is also expected that the responses will be transcribed to the eCRF via MACRO v4 on the same day as the patient completes them.

6.2 Data Entry

The DEFeND Trial uses two web based electronic data capture systems, TARDIS (Treatment Allocation Randomisation System) and MACRO v4 database for remote data capture (RDC). (See Site Randomisation, Registration Instructions and MACRO User Guide for more details on both of these systems).

A delegated member of staff at site will input the data in real time using their own unique username and password:

- The delegated member of Site staff logs onto the client or web interface of MACRO using their username and password. See section 7.
- The delegated member of site staff will input data in real time.
- If not already done as part of the registration process, a new subject in the DEFeND trial is created. The visit schedule is then displayed. The subject number used in MACRO is made up of site number and patient number in numerical order. If the subject has already been created, they will be available for selection from the subject list.
- The delegated site staff member selects on MACRO the form corresponding to the patient encounter. They then enter information onto the database using the text boxes and option buttons, adhering to the rules described in sections 6.2.1 – 6.2.9.
- Once all data is entered, the delegated site staff member clicks save button to save the form to the MACRO database.
- Users must remember to log out from the database. *See section 7.*
- The DM will view 100% of the incoming data in order to be able to raise queries with data in timely manner (within 14 days of data being entered onto MACRO by site)

6.2.1 Forms to be sent to LCTU

The only paper forms the LCTU are collating from site are the SAE and pregnancy reporting forms

6.2.2 Abbreviations and spelling mistakes in CRFs.

Obvious spelling errors in medication and medical terminology can be 'self-evident corrected' providing there is no doubt as to what the entry should be. A comment stating SEC should be added to MACRO next to the data that has been corrected. If an abbreviation is not known at the LCTU, a data query should be raised.

6.2.3 Missing Data.

All fields left blank on eCRF forms, must be data queried unless clearly not applicable (e.g. results of pregnancy test for a male patient). Any data fields recording primary or secondary end point information will be mandatory fields on the MACRO database, i.e. the researcher will not be able to leave fields incomplete. Fields with no information in will be data queried by DM upon 100% check of entered data.

6.2.4 Use of "NK" in date field.

MACRO will not allow the entry of text into the date field, the following set of rules must be followed.

- Unknown day e.g. NK/06/2006 – The NK will be replaced with 15.
- Unknown month e.g. 01/NK/2006 – The NK will be replaced with 06.
- Unknown day and month e.g. NK/NK/2006 – The date of 15/06/2006 will be used.
- Unknown day, month and year e.g. NK/NK/NK. No date will be entered.
- Start day of an event is unknown but end date is known and is before 15th of the month. As it makes no sense to have a start date of an event *after* its end date, in such circumstances the day in the start date is recorded as half of the end date
    - (e.g. start of event NK/06/2006, end of event 14/06/2006). If start recorded as 15/06/2006 it is *after* the end, therefore record start date as 07/06/2006).

6.2.5 Units.

- Re-scaling – The delegated site staff may carry out re-scaling of units (e.g. from g to mg) only if the stated units are entirely unambiguous. If re-scaling is performed the delegated

site staff must add a comment in MACRO stating the original result (with units) recorded in the workbook.

- Conversion – e.g. from lb to kg. This can only be done at the discretion of the site, as with re-scaling, and a comment must be added to MACRO. If there is any scope for doubt a data query must be raised.
- Missing Units – Must be data queried.

6.2.6 Out of Range Values

An acceptable range of values can be set for fields when developing the MACRO database for a particular trial. If a value provided on eCRF is out of range, MACRO will raise a warning when it is entered onto the database. Data queries should be raised for all values that are out of range. If a warning is raised at the time of entry at site, a note must accompany this warning. If no note is available when the DM checks the data entered, a query will be raised asking for a note to explain the out of range value to be added to MACRO.

6.2.7 Incorrect use of answer codes

Some questions may ask for a numerical answer referring to a multiple choice code. If the answer is written in words instead of using the code (e.g. "oral" is written instead of a number code for a question relating to route of drugs taken), provided the answer is clear and unambiguous, it can be permitted with a comment added to MACRO stating what the actual data was.

6.2.8 Protocol deviations.

Protocol deviations, e.g. Incorrect timing of randomisation. All protocol deviations (along with corrective and preventative actions if applicable) are recorded in DEFeND Site Status within the Trial Management System. Once the deviation is created and saved, a copy is printed, signed and dated by the author and counter-signed and dated by the Chief Investigator. This is filed in the site file and patient file if applicable.

6.2.9 Date/Time Stamps.

As well as the Server time, MACRO uses the date and time that is set on the user's local computer (to account for geographical differences).

N.B. If sites adhere to the "CRF Completion Guidelines" it should result in fewer queries requiring clarification. Consistent deviation from these guidelines should be raised with the relevant site and further training considered.

7 Database Locks

The database will need to be locked at time points during the study, for example prior to interim and formal analyses.

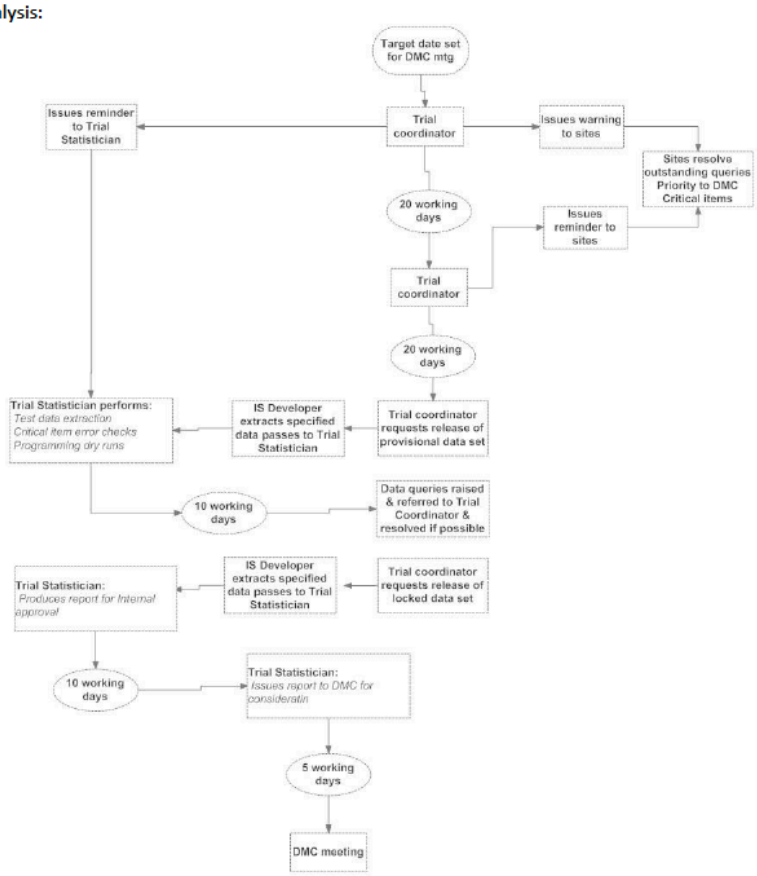
Each database lock must be formally authorised. The TC should complete an IS-D006 Data Extract Request Form, which must be signed by the Chief Investigator (CI). This Form is then forwarded to the Information Systems team, at least 1 month prior to the requested database lock date.

Once the date for a database lock is confirmed, the DM/TC should inform participating trial sites of the impending data lock, and request that sites send as much outstanding data to the LCTU as possible. A special effort should be made to ensure entry of CRFs and Data Query responses onto the database are up-to-date prior to a data lock.

A provisional data lock may be requested by the Trial Statistician to:

- Ensure any missing/seemingly inaccurate data has been appropriately data queried so that the response can be gathered from the site prior to full database lock
- Develop programmes to create the tables specific to the analysis type.

The diagram below shows the activities to be completed prior to each data lock and subsequent analysis:



8 Security

To ensure the database is only updated or amended by authorised individuals, the data entry system requires users to have a username and password, to be entered at the start of each data entry session.

Users should log out of the data entry system each time they leave their work station unattended. Each computer station should be set to revert to a password protected screen saver mode when left idle for 10 minutes.

Individuals should only work under their own username and **should not log anyone else onto the system.** The MACRO database package has several methods built in to maximise security:

- Each password must contain between 6 and 15 characters, including lower and upper case letters and at least 1 number.
- If left idle for 20 minutes MACRO automatically locks out the user, who must then re-enter their password to regain access to the database. .

9 Audit Trails

MACRO records any changes made to data in the system, and all user activity is logged. For a particular question, the audit trails consists of a chronological record of the status, response value, warning messages and overrule reasons, reasons for change, comments and lock status.

Whenever any of these items are changed, a record is kept of the date and time, and the username of whoever made the change. Users with appropriate permission have access to view audit trails, however no-one is able to change or delete an audit trail. The audit trail allows the LCTU to monitor the quality of individual team members' data input, and highlight training needs if consistent errors are found.

10 Dealing with data queries

Please refer to SSDEF_D016 – DEFeND Data Query Plan

11 Adverse Event and Serious Adverse Event Reporting

SAEs as defined by the protocol, encountered during the trial will be reported Using paper SAE forms. Please refer to the DEFeND Safety Plan SSDEF_D009 – DEFeND Safety Plan. Data management rules outlined in described in sections 6.2.1 – 6.2.9 still apply to the data on SAE forms.

12 Quality Assurance

Quality Assurance (QA) is the prevention, detection and correction of errors or problems. QA is closely tied to Good Clinical Practice (GCP). A key requirement of GCP is the documentation of what has occurred during the study. This DMP helps to fulfil this requirement by creating a Data Validation Plan and detailing what documents will record the conduct of the study. *(Please see Trial specific the Data Validation Plan and Report. The purpose of these documents is to validate the data set on the DEFeND MACRO database.)*

Quality Control (QC)
QC of the all trial databases will be conducted in accordance with SOP DM006 QC of Trial Databases.

13 Communication Logs

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for, amongst other things, the recording of communications relating to trials that involve the participation of human subjects. Thus, all verbal (i.e. telephone) communications with sites regarding the trial and/or participants and/or data that are deemed *significant* by the Senior TC need to be logged. In particular, following conversations where it is apparent that a site's ability to comply with the protocol and/or provide accurate data is impaired, details of the conversation should be logged as a file note within the Trial Master File, with a copy place on the patient's file.

14 Training

All LCTU staff using MACRO will receive appropriate training, documented in each individual's training folder held in the LCTU. The MACRO training covers:

- Data Entry.
- Data Reporting
- Batch Validation.

All staff must be added to the central delegation log, and signed off as approved by the CI, before entering any data onto the MACRO database.
TC will be provided with a copy of the MACRO training manual, produced by the DD *(See INS_D008 MACRO 4 User Guide).* The MACRO DD has had extensive MACRO training. If any updates are implemented to MACRO a training session is organised and co-ordinated by the DD.

15 Archiving of Database

The DD will organise the archiving of the database once the data have been analysed in accordance with SOP IS013 - Study Closedown and Archiving

16 Data Management Responsibilities (Task Delegation Log)

Task	Responsible for the task	Who is performing the task	Comments/ description
CRF and protocol amendments	PhD student	PhD student	In consultation with the Statistician and CI
Data Management Plan	PhD student	PhD student	The DMP has been designed as a working document, and so it is expected that this will be updated throughout the trial. Amendments made to the DMP will be made by the Document Controller to ensure accurate version control, archiving and

			the distribution of current documents.
Design and programming of database, screens and edit checks	PhD student	PhD student	In consultation with supervising DD
CRFs on MACRO	PhD student	PhD student	In consultation with supervising DD
Test of database/ screens / edit checks	PhD student	PhD student	In consultation with supervising DD
Data entry guideline	PhD student	PhD student	
Application implementation process	PhD student	PhD student	
Data entry	NA	NA	
Edit check process	PhD student	PhD student	In consultation with supervising DD
Data Query process	PhD student	PhD student	
Edits in the database according to queries	PhD student	PhD student	
QA of data	PhD student	PhD student	In consultation with supervising DD and statistician
Db release / freeze	PhD student	PhD student	In consultation with supervising DD
Data handling report	PhD student	PhD student	In consultation with supervising DD
Transfer of database to statistician	PhD student	PhD student	In consultation with supervising DD

17 Acronyms and Definitions

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DD	Database Developer
DM	Data Manager
DMP	Data Management Plan
EU	European Union
EudraCT	European Union Drug Regulatory Authorities Clinical Trials
GCP	Good Clinical Practice
ICH	International Conference of Harmonisation
ISDMC	Independent Safety and Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
LCTU	Cancer Research UK Liverpool Cancer Trials Unit
NK	Not Known
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RDC	Remote Data Capture
SAE	Serious Adverse Event

SEC	Self-Evident Correction
SOP	Standard Operating Procedure
SQL	Structured Query Language
SSL	Secure Sockets Layer
TC	Trial Coordinator
TM	Trial Monitor

A.8 Monitoring Plan

DEFeND

MONITORING PLAN

Author: MANDEEP BAJWA **Signature:** [signature] **Date:** 01/10/2018

Reviewer: ZIVIWONE GORE **Signature:** [signature] **Date:** 01/10/2018

Acknowledged: ANDREW SCHACHE **Signature:** [signature] **Date:** 02/10/2018.
(Chief Investigator)

Acknowledged: Richard Jackson **Signature:** [signature] **Date:** 01/10/2018
(Statistician)

Authoriser: S. Chauhan **Signature:** S Chauhan **Date:** 02/10/2018.
(LCTU Operational Director / Deputy Director)

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1. Introduction

Trial monitoring is carried out to ensure that the rights, safety and well-being of human subjects are protected during the course of a clinical study. Also, that the reported trial data are accurate, complete and verifiable from source documents. It is also essential to ensure that the trial is conducted in compliance with the current approved protocol, SOPs, ICH GCP and regulatory guidelines.

The purpose of this trial monitoring plan is to outline the procedures that will be undertaken during the monitoring of the DEFeND trial to ensure adherence to the requirements stated above.

This plan will be a working document and will be updated throughout the course of the trial should amendments become necessary. This will be the responsibility of the Trial Co-ordinator (TC) and will be reviewed every 6 months. Amendments made to the plan will be made through the Document Controller to ensure accurate version control, archiving and the distribution of current documents.

2. Protocol Summary

A neck dissection is an operation to remove the glands in the neck either because they have cancer in them or they are at risk of cancer spreading to them. Complications after neck dissection are a significant problem for patients and may affect their quality of life. Research on understanding the feelings of patients who have had head and neck cancer, has shown that avoiding complications is very important to them.

We have found evidence that by giving patients a substance that copies the blood clotting process called Fibrin Sealant, we may be able to protect them from complications. This is because this substance can seal areas of bleeding and stick the raw surfaces of the wound together. Unfortunately, there is no high-quality research that has been able to answer whether Fibrin Sealants can prevent complications after neck dissection. Therefore, we have designed a clinical trial to help us answer this important question. However, before this can be started we need to conduct an external pilot study to make sure it has been designed in the best possible way.

Patients who are due to have a neck dissection, are over 18 years old and have capacity to consent will be included in the study. We will exclude patients who may be pregnant or may have an allergy to Fibrin Sealant.

This study will be conducted in Aintree University Hospital and Queen Victoria Hospital and will last for 12 months. Participants will be randomised to either receive Fibrin Sealant during their surgery or have their surgery as normal without it. The main questions we aim to answer are:

1. Can we recruit patients?
2. Do all aspects of the study design work well together?
3. How many patients do we need in the 'full' trial?

3. Trial Monitoring Responsibilities

The DEFeND study is sponsored by the University of Liverpool who have delegated trial monitoring to the Liverpool Clinical Trials Unit (LCTU). The Sponsor will review all monitoring reports (central) to ensure sufficient sponsor oversight and that the trial is being conducted in accordance with the current research legislation.

The Trial Management Group (TMG) will include the CI, PhD student (roles include Trial Co-ordinator (TC) and Data Monitor (DM)), PhD supervisors, Trial Statistician, Senior Trial Co-ordinator and Sponsor Representative. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly.

Trial Co-ordinator (TC): It is the responsibility of the TC to perform central monitoring procedures according to this plan. The TC will carry out and report any triggered monitoring visits according to this procedure. The TC will carry out source data verification during triggered visits as applicable.

Senior Trial Co-ordinator (STC): It is the responsibility of the STC to review the monitoring visit schedule and the recruitment rate of each site and to review and approve the monitoring visit reports and follow up letters. The STC may organize, carry out, and report the monitoring visit according to this procedure, in the absence of the TC.

LCTU Operational (Deputy) Director: In the absence of the TC or STC or if the monitoring visit has been performed by the Trial Co-ordinator the LCTU (Deputy) Operational Director will be responsible for review and approval of the monitoring report.

4. Extent of Monitoring

With respect to the extent and nature of monitoring ICH GCP states that:

> *"The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general, there is a need for on-site monitoring, before, during and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."*
>
> ***ICH E6 (R2) (2016, Section 5.18.3)***

Trial Steering Committees, Data Monitoring Committees and similar, oversight committees, can also be considered as a form of monitoring (MRC/DH 2004). ICH GCP-E6 is not specific about which format monitoring should take in conducting clinical trials but consideration of how complex the trial is, and the risks associated with running the trial should be factored into the decision (E6 (R2), 2016, Section 5.18.3).

As per standard LCTU practice (SOP TM005 Risk Assessment) and sponsor standard practice a structured risk assessment was carried out for the DEFeND trial in order to assess the extent of monitoring required relative to the risk. It was agreed between the sponsor and the LCTU that the LCTU risk assessment be followed in the management of this trial. The DEFeND trial is a Type A – comparable to the risk of standard medical care and the risk assessment score indicated this is a low risk trial.

DEFeND does not involve any IMP, and the use of ARTISS fibrin sealant (intervention) is considered a safe procedure. It was considered that being a Type A study central monitoring, with triggered monitoring visits, is a sufficient way to monitor the trial and risk associated with it.

4.1. Trial Oversight Committees

The responsibilities of the Trial Steering Committee (TSC) are outlined by its respective charter SSDEF_D012 – DEFeND RSC Charter.

4.2. Central Monitoring

The DEFeND trial will use central monitoring. The TC and CI are mainly responsible for the central monitoring processes, although this could be delegated as appropriate. The TC or delegate will produce

monthly central monitoring reports which will be reviewed by the Chief Investigator (CI), the sponsor and TMG, to ensure an accurate understanding of the sites' compliance with the study protocol.

5. Procedures for Monitoring

5.1. Site Initiation Visits

The site should be initiated according to SOP TM036 - Study Initiation Meeting.

The site should be opened to recruitment according to SOP TM043 - Trial Site Greenlight Process

5.2. Scheduling and Preparation for Triggered Monitoring Visits

On-site monitoring visits may be triggered by the TMG as a result of findings from the review of central monitoring of data and the reason clearly documented in the monitoring report. It will be the responsibility of the TMG to decide if further unscheduled monitoring visits are required. This opinion should be clearly documented in the visit report. The TC will conduct the visit.

The following 'triggers' for on-site monitoring will be reviewed and the list below is not exhaustive. There may be other factors that require consideration when deciding to perform a site visit.

- Identification of clear differences in recruitment rates between sites or no recruitment at a site for an extended period, as specified in the monitoring plan
- Repeated non-receipt of consent forms within the timelines specified in the protocol
- Repeated use of superseded versions of the Patient Information Sheet and Consent forms (PISC)
- Repeated inaccuracies in the completion of consent documentation, despite contact to rectify initial discrepancy
- Repeated violations in the timing of consent and trial related procedures, despite contact to rectify initial discrepancy (SOP TM037 Identification and notification of serious breaches of GCP or trial protocol)
- Repeated evidence of recruitment of ineligible patients
- Repeated discrepancies in the assignment of randomisation number at a given site
- Inappropriate delegation of responsibilities or repeated undertaking of tasks by individuals not delegated the responsibility.
- Persistently inadequate quality of completion of the CRFs or persistent failure to send CRFs to LCTU in a timely manner.
- Screening failure rates at a particular site in excess of others when rates compared between sites.
- Persistent non-receipt/transfer of CRF pages for the randomisation visit.
- CRFs repeatedly not signed off in a timely manner or in accordance with the protocol.
- Persistent missing non-source data.
- Persistent discrepancies between source data and CRFs.
- Continually not being up to date with CRF completion and persistent non-receipt of CRFs.

- Persistent inadequate/non-response to data queries.
- A higher than average number of data queries.
- Identification of significant and/or persistent non-compliance with the protocol on the part of the PI or other members of the research team.
- Where there are poor SAE reporting levels at site in comparison with the study as a whole.

The TC or designated person who conducted the visit will complete a report detailing the reason for the visit, data monitored, processes reviewed, issues identified and discussed with the study staff at the visit, as well as corrective measures to be implemented, if applicable. Any outstanding action item from the previous visit will be followed up and documented on the monitoring report, if applicable. The report should be prepared within 10 working days after the last day of the visit. The report will be reviewed and signed by the Trial Co-ordinator or Senior Trial Monitor within 10 working days once submitted.

After every monitoring visit the TC or designated personnel should forward a follow-up letter to the Principal Investigator, ensuring that a copy is forwarded to other site personnel present during the visit. This should outline any issues identified during the monitoring visit and suggested or agreed remedial actions if applicable. Also, any discrepancies identified from the source data verification (SDV) which were not able to be resolved at the time of the visit, are raised as queries on the database and either sent with or highlighted in the follow-up letter. Where issues relate to data quality, recruitment, patient safety or trial progress, correspondence should also be directed to the PI.

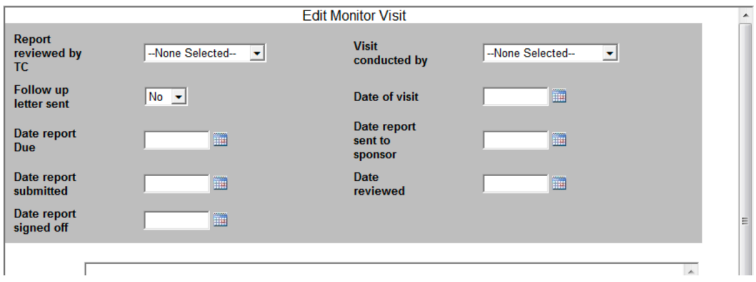
Finalised monitoring visits reports and follow up letters should be transferred onto the LCTU portal sponsor section.

Once the follow up letters have been sent and the finalised monitoring reports uploaded on the Sponsor Section of the web portal, the TC will update the Site Status database with the following;

- Date of actual visit
- Date report submitted
- Date report reviewed
- Date report signed off
- Date report sent to sponsor

5.3. Recording Monitoring Visits

Once the visit has been scheduled, the person conducting the visit is responsible for ensuring that the monitoring section of the site status database is updated (as per below).



5.4. Managing Cancelled Monitoring Visit

Visit to site may be cancelled due to severe weather conditions, change in Monitor, on site request or other unforeseen circumstances. The Trial Monitor/TC should document on Site Status the reason the visit did not take place. Communication with site regarding the cancellation, e.g. email to/from site should be put on file and also saved in the specific site email folder. Arrangements should be made to visit site at the earliest possible time.

5.5. Central Monitoring

Monthly central monitoring review to check on protocol compliance, randomisation compliance, follow up compliance, data submission, SAE reporting, recruitment including screening , enrolment, randomisation and serious breaches will be performed by the TC.

5.5.1. Goals

- To review data collected within the trials unit
- To assess site performance in relation to data returns and quality, compliance with GCP, safety reporting and translational sample collection
- Identify problems early and direct monitoring resources appropriately

5.5.2. Production of report and scheduling TMG review

The DEFeND central monitoring report will be produced every month and will start 1 month after study greenlight and cease after final data lock.

Reports should be produced around 1 week prior to the scheduled TMG meeting and circulated to all TMG members ahead of the meeting. The minutes of the TMG meeting, summaries of discussion and actions should be recorded on the report prior to sign off by the CI. The signed report will be uploaded to the portal and saved within the electronic Trial Master File by the TC.

5.5.3. Managing cancelled TMG meetings

If for any reason the TMG are unable to meet in person the report review will be conducted by email. Email correspondence must be stored with the report and the CI will have final say on the actions for that period. The same time frames as section 5.5.2 apply.

5.5.4. Central monitoring metrics

The following will be shown in the report:

- Overall recruitment (target and actual)
- Site recruitment
  - Number of patients screened
  - Number of patients registered
  - Number of registration problems
  - Number of patients randomised
  - Number of randomisation problems
- Withdrawals
  - Number of withdrawals and reason, overall and per site
- Safety
- Serious breaches
- Protocol deviations
- Data queries
- Translational samples

5.6. Recruitment and Withdrawals

The following will be recorded monthly:

The recruitment data will be reviewed against rates forecast as documented in the grant applications

- Overall Recruitment (Target and Actual)
- Site Recruitment
  - Number of patients screened, and screen failures
  - Number of patients randomised
  - Number of registration problems
- Withdrawals
  - Number of withdrawals and reason, overall and per site

Screening data will be collected via the LCTU web portal.

If the site has not recruited:

- The research nurse at site should be contacted to ensure their screening logs are up to date. It should be ascertained whether the site is having difficulties recruiting patients (i.e. less than 2 patients per month) and the reasons for this. Any actions discussed should be given a realistic timescale for implementation. If there is still no improvement, the TC or CI should contact the PI to discuss the issues further.
- The CI will be informed of poor recruitment during TMG meetings.
- Site screening and recruitment figures are to be reported to the Sponsor via the Central Monitoring Report. All discussions and proposed actions with sites should be confirmed by email and a copy filed in the ISF.
- If any site continues to recruit poorly after any actions have been implemented the TC and CI should discuss its possible closure.

5.7. Informed Consent

- Any consistent problems with consent during enrolment.

The completed patient informed consent form (ICF) should be uploaded to the LCTU portal for two independent central checks by the DEFeND trial team. This check should include the following:

- The ICF was signed and dated correctly by the patient or their representative
- The patient initialled against each statement of the ICF.
- The most up-to-date version of the ICF was used and printed on trust letter headed paper.
- The correct version numbers of the signed ICF and PIS handed to the patient are transcribed into the MACRO database.
- The person taking consent is on the site delegation log and has permission to do so.

Each member of the trial team that has checked the consent can authorise the validity of the consent on MACRO. Both independent checks must confirm validity of the ICF before MACRO will allow the patient to be randomised. Any significant and/or persistent non-compliance with informed consent requirements that are identified should be highlighted to the site. The TC will inform the Chief Investigator and Trial Sponsor as necessary. Suspected serious breaches of either the protocol or clinical trials regulations will be handled as per SOP TM037.

5.8. Safety

Central Monitoring. The following will be recorded monthly:

1. Serious Adverse Events (SAE)
   a. Number of SAEs per total patient and per site

2. Suspected Unexpected Serious Adverse Reactions (SUSARs)
   a. Line listings of all SUSARs: site, patient number, date, severity and description

The totals of the above will be reviewed in LCTU Business Meetings, and by the TMG and TSC.

Any significant differences in the reporting rates of AEs, SAEs or SUSARs will be discussed within the TMG, who will decide if any further action should be taken.

Upon initial submission, a review should be made by the person handling the SAE report to ensure that it has been reported and reviewed by someone with the appropriate experience, and who is assigned the task on the delegation log.

5.9. Protocol & Regulatory Compliance

A Protocol Deviation is any clinical intervention, act or omission that occurred either in error, or intentionally, that does not adhere to the current trial protocol that is in use by site.

Central Monitoring:

1. Serious Breaches
   a. Line listings of all Serious Breaches: site, patient number, date, severity and description

2. Protocol Deviations
   a. Line listings of all Protocol Deviations: site, patient number, date, severity and description. These will be sent to site as and when they occur.

3. Corrective / Preventative Action Forms raised against the study

Any deviations noted during data entry review should be recorded on a Protocol Deviation Form on the portal. This will be highlighted with the STC to avoid any duplication.

Protocol deviations should be graded by the Chief Investigator (or TMG) in terms of the impact such a deviation would have on the risk of introducing bias in the trial results. This is generally graded as major (in which case patients who experience this protocol deviation would be excluded from any "per protocol" analysis set) or minor (in which case patients who experience this protocol deviation would be included in the "per protocol" analysis set), but the grade may vary according to the degree of deviation observed. Justification should be provided for the assessment of the impact of each potential protocol deviation.

Any significant and/or persistent non-compliance on the part of the Investigator or other study staff members that are identified during central monitoring will be discussed within the TMG to confirm if any further action is required. Suspected serious breaches of either the protocol or clinical trials regulations will be handled as per SOP TM037

5.10. Source Data Verification

Although formal monitoring visits are not routine, source data verification (SDV) of the primary end point (surgical complications) will be performed routinely for the purposes of Quality Assurance (QA). The SDV for QA will involve the TC visiting the site at 3 monthly intervals and comparing the data recorded in MACRO to the patient's case notes. **This will not constitute a formal monitoring visit**. No source documents will be stored in the LCTU The reason for this exception being that this process will inform the pilot/feasibility outcomes of the DEFeND trial. The underlying objective of source document verification is to ensure accuracy of the data and validity of the primary and secondary efficacy and safety variables for the study.

Source data verification is achieved by systematically checking that each value entered into fields within the CRF can be verified against source data as described by ICH E6 (R2) 1.52 (See below).

The Trial Monitor should always use **primary source data** to verify data in the CRF. Primary source data includes:

> "Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)"
> (ICH E.6 (R2), 2016, section 1.52)

In addition to verifying that data is accurate and verifiable, it is the responsibility of the TC to ensure that the data captured within the eCRF is compliant with the trial protocol.

5.11. Case Report Forms

The DEFeND trial is designed to use eCRFs on the MACRO database to collect all patient data. eCRFs are to be completed and data entered by a delegated person who will have MACRO permissions and be provided with their unique login details for the system. Research staff at site should upload the data to the MACRO database in real time i.e. on the same day as visit. The TC will check 100% of data entered by sites and raise queries as necessary. An automated email generated from MACRO will go to the site who can then correct their entry directly onto the database. The TC will close the query when it has been answered satisfactorily. Any data queries should be raised and completed within **three weeks** of the data being entered onto MACRO. Please refer to **SSDEF_D016 – DEFeND Data Query Plan** for more details.

Using the eCRF system ensures data can only be entered by research staff who have been delegated data completion on the delegation log, via their unique login details. This data will be checked at LCTU by the TC for discrepant or invalid data. The trial MACRO database will be developed with a series of in-built computer validation checks, either flagging or preventing entry of invalid data. Any missing forms of data will be chased by the DM as a data query.

The following will be recorded monthly:

1. Missing Case Report Forms (eCRFs)
    a. Number of missing eCRF (defined by the schedule above, without justification/notification of visit delay)
    b. Number of missing eCRFs per total patient

If the site is behind schedule with eCRF completion by more than 2 working days, the TC will work with the site to develop a plan to correct this issue and will ensure the CI and other relevant trial staff of any delays and associated issues.

5.12. Data Queries

Please refer to **SSDEF_D016 – DEFeND Data Query Plan** for details. For all triggered monitoring visits, the TC should take any outstanding (whether open or re-raised) data queries. The site should respond to the queries by completing the individual discrepancy report. The TC should aim to SDV all data queries related

to primary endpoint at the time of visit. The TC should bring the original data clarification form back to the LCTU, and a copy should be left at site appended to the eCRF page the query relates to.

A listing of 'responded' data queries for patients should also be taken to the visit in order to SDV responses and assess whether the queries can be closed or re-raised.

The following will be recorded monthly:

1. Data Queries
    a. Number of data queries per total patients and site
    b. Number of unresolved data queries per total patients and site
    c. Type of queries raised per total patients and site

5.13. Personnel

Study staff can include anybody detailed on the delegation log to perform activities concerned with the conduct of a clinical trial. These staff members include, but are not limited to:

- Principal Investigator (s) (P.I)
- Co / Sub – Investigator (s)
- Study Site Coordinator
- Data Manager
- Research Nurse
- Research Radiographer
- Trial Pharmacist

As part of the Greenlight process (TM043), the TC or delegate should ensure that there is a recently signed CV and GCP certificate for all who are listed on the delegation log. Throughout the trial, it will be the responsibility of the TC to request and collect CVs and GCP certificates for new members of staff that have started on the trial, updated delegation log or any updates, as well as any training documents or certificates which provide evidence that staff have received adequate training in the study. It may be appropriate for any requested CVs and GCP certificate to be collected during a monitoring visit instead of the site sending them to the LCTU.

5.14. Communication with Sponsor

Communication with the sponsor will take place under the following circumstances:

- **Information regarding recruitment and withdrawals**
    - A representative of the Sponsor will regularly attend TMG meetings where recruitment and withdrawals figures will be presented and discussed. The Sponsor will also be able to view the Central Monitoring Report via the LCTU portal.
- **Breaches in protocol and/or regulatory compliance**
    - Suspected serious breaches of either the protocol or clinical trials regulations will be handled as per SOP TM037. This documents that as soon a serious breach has been notified to any member of the LCTU, it should be immediately reported to LCTU Operational Director, TC, Chief Investigator and Sponsor. The initial reporting should include:
        - Full name of trial title and protocol number.
        - Name of CI and Principal Investigator at the site where the suspected serious breach occurred.

  - Details of suspected serious beach, including patient identifier(s) details, if applicable (initials, Screening/Randomisation number, Date of Birth, but NOT patient ('s) name(s)).
  - Details of any initial corrective actions already implemented.
  - Once provided, the initial details should be documented on the Serious Breach Assessment Form and this should be forwarded to the sponsor so that they can provide input to the assessment of the incident.
- **Missing data**
  - Any issues with missing data will be documented in the central monitoring report, which the sponsor has access to.

5.15. Translational

The following will be recorded monthly:

- Number of patient consent for samples, and any samples sent without consent
- Number of samples sent
- Sample Quality
- Any problems with the samples.

The Trial Co-ordinator will discuss any persistent problems identified with the site, and discuss any further action needed.

5.16. Investigator Site File

The ISF is the responsibility of the site to maintain. All documents required for the site will be available from the LCTU website.

5.17. Continuing Acceptability

The TC will review the continuing acceptability of the site as follows:

- The resources and involvement of the Investigator, and the facilities remain adequate to safely and properly conduct the study
- Any site personnel changes are recorded on the appropriate study documentation and an up to date staff site task and delegation log completed.
- Any problems are addressed and discussed with the Investigator/site personnel and appropriate action taken

The Investigator and staff remain adequately informed about the trial and are performing the specified trial functions in accordance with the protocol and other agreements and have not delegated these functions to unauthorized personnel.

It is the responsibility of the TC to ensure that a request is made to the appropriate member(s) of study staff to set aside time at triggered monitoring visits. Depending on the reason for the triggered visit it may be necessary to review appropriate trial documentation, discuss progress of the trial, and review data clarification forms, or to ensure that new members of staff receive appropriate trial specific training which are documented on training records and are captured on the site delegation log.

6. Post Monitoring Activities

After every monitoring visit the TC should forward a follow-up letter to the CI, ensuring that a copy is forwarded to other site personnel present during the visit. This should outline any issues identified during the monitoring visit and suggested or agreed remedial actions if applicable. Also, any discrepancies identified from the SDV which were not able to be resolved at the time of the visit, are raised as queries on the database and either sent with or highlighted in the follow-up letter. Where issues relate to data quality, recruitment, patient safety or trial progress, correspondence should also be directed to the CI.

Finalised monitoring visits reports should be transferred onto the LCTU sponsor portal.

7. Close Out

Sites should be closed if patient enrolment and study participation is completed, all eCRFs are completed and collected, and all data queries are resolved. The site may also be closed if the site has not enrolled any patients for a considerable amount of time and the enrolment rate is not acceptable, if the site is non-compliant with study procedures or regulatory requirements, or the study is terminated for any reason.

The purpose of a site closure is, but not limited to:

- Performing a final review of the regulatory documents, study data (eCRFs and data queries), to make sure that the site's records are sufficient.
- Ensuring that all AEs and SAEs have been followed-up to completion.
- Ensuring that all study IMP and study-specific equipment has been removed from the site.
- Ensuring that the centre has complied/is aware of the need to comply with any ICH-GCP, EC & local regulatory requirements.
- Ensuring the ISF is complete and contains current documentation, including the Pharmacy Site File.
- Reviewing all the patient accountability logs that they are up to date.
- Reviewing the ISF documentation that it mirrors the site specific TMF.
- Arranging document archiving with site.
- Sites will be closed as per SOP TM023 Trial Site Closure.

A.9 Safety Plan

LIVERPOOL CANCER TRIAL UNIT - SAFTEY PLAN

Title of Clinical Trial: **DEFeND** – Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

REC Ref Code: 18/NW/0209

IRAS No: 234851

CI: Andrew Schache

Sponsor: University of Liverpool

This safety plan details the procedure to be followed by the Liverpool Cancer Trials Unit (LCTU) staff on receipt of an SAE form (Appendix 1) for patients on the DEFeND trial.

1 LCTU Reporting Responsibilities:

- Maintain detailed records of all SAEs occurring on the DEFeND trial reported by Principal Investigators (PIs) across all research sites as specified in the trial protocol and in accordance with the regulatory requirements.
- Ensure that all SAEs (other than those specified in the protocol as not requiring immediate reporting) are promptly assessed (within 10 days) for causality, grade and expectedness by the Chief Investigator (CI) or delegated qualified other (Clinical Coordinator (CC)).
- Upload SAE reports and where expedited, the HRA Report of Serious Adverse Events for non-CTIMPs as and when they occur to the sponsor area of the Portal.
- Provide line listings of all SAEs reported on the trial to the sponsor every 6 months via email. Reporting of all expedited cases (e.g. unexpected and related to the trial intervention) to the appropriate Research Ethics Committee (REC) within 15 days of receiving the SAE. Any additional relevant information should be sent as follow-up information as and when it becomes available.
- Inform all local PIs of expedited SAEs that occur on a monthly basis.
- Notification of any urgent safety measures taken to the appropriate REC, sponsor and the local principal investigators within 3 days.
- Perform monthly central monitoring of SAE reporting rates across sites.
- Maintain a safety reporting calendar to ensure there is always cover by a TC and CC.
- Maintaining the list of expected events within the protocol and updating as required. Ensuring CCs are provided with current versions of the expected events.

2. Recording and reporting of Adverse Events

Surgical complications and adverse reactions to ARTISS fibrin sealant that are Clavien-Dindo grade IV or above (see **Table 1**) will be the only events **reported** to assess safety. As the 'Clavien-Dindo Classification of Surgical Complications' constitutes a primary outcome measure for the DEFeND

trial, the presence of post-operative complications along with their grade will be **recorded** on the eCRF.

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
	Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info

Table 1. Clavien-Dindo Classification of Surgical Complications (Clavien PA et al. Ann Surg 2009; 250: 187 – 96).

3. Recording and reporting of SAEs, SARs, SUSARs and other expedited SAEs

All SAEs should be recorded in the patients' hospital notes by investigators. **Only the following events should be reported to the LCTU, in accordance with the trial protocol:**

- Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above (see **Table 1**).
- An exacerbation of a pre-existing illness/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant that is Clavien-Dindo grade IV or above (see **Table 1**).
- An increase in frequency or intensity of a pre-existing episodic event/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant that is Clavien-Dindo grade IV or above (see **Table 1**).
- A condition (even though it may have been present prior to the start of the trial) detected after the trial surgery and/or use of ARTISS fibrin sealant that is Clavien-Dindo grade IV or above (see **Table 1**).
- Continuous persistent disease or symptoms present at baseline that worsens following the trial surgery and/or use of ARTISS fibrin sealant that is Clavien-Dindo grade IV or above (see **Table 1**).

The following events should <u>not</u> be reported to the LCTU, in accordance with the trial protocol:

- Events including signs, symptoms and disease that are not deemed a complication of the trial surgery as per the definition above.
- Generalised signs and symptoms of having undergone major head and neck surgery e.g. lethargy, difficulty with speech and/or swallow.

- Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien Dindo grade IIIb or below (see **Table 1**). *These will be recorded in the eCRF as an outcome measure*.
- Extended hospital stay due to a delay in planned surgery.
- In-patient hospitalisation or prolongation of existing hospitalisation due to post-operative complications that are grade IIIb or below (see **Table 1**).
- Medical or surgical procedures - the condition which leads to the procedure is the SAE.
- Pre-existing disease or conditions present before surgery that do not worsen.
- An exacerbation of a pre-existing illness/condition that is not deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- An increase in frequency or intensity of a pre-existing episodic event/condition that is not deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery.
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.
- Injury or accidents.
- Abnormal laboratory results.

All complications related to the neck dissection surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above must be reported as SARs, SAEs and SUSARs. They should be reported within 24 hours of the local site becoming aware of the event up to 6 weeks post-surgery. SARs, SAEs and SUSARs may be reported past 6 weeks if deemed appropriate to do so by the local investigator (e.g. the complication is considered to be related to the trial surgery). The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the complication has not resolved at the time of reporting.

All complications related to the neck dissection surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IIIb or below that meet the definition of serious are exempt from SAE reporting. Such events should only be recorded in the relevant section of the eCRF.

Post-operative complications related to either neck dissection or use of ARTISS fibrin sealant that are Clavien-Dindo grade IIIb or below are **expected** for the DEFeND trial.

Post-operative complications related to either neck dissection or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above are **unexpected** for the DEFeND trial.

The LCTU will notify the main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and/or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Site staff (with the exception of the surgical team) will be blinded therefore the SAE form will not state which arm the patient has been randomised to. For the purposes of SAE reporting it should be assumed that the patient was randomised to **receive** ARTISS fibrin sealant (i.e. interventional arm). Causality should be assigned to the following:

1. Anaesthetic
2. Generality of surgery (including surgical airway, primary tumour resection)

3. Neck dissection surgery
4. Use of ARTISS fibrin sealant

3.1 Steps for Reporting

SAEs should be reported by completing a hard copy Serious Adverse Event Form **(Appendix 1)** and faxing or emailing this to the DEFeND trial team. Blank SAE forms for this trial are available to download from the LCTU portal (www.lctu.org.uk/). In addition to this the a high priority email should be sent to the TC (msbajwa@liverpool.ac.uk).

The LCTU will acknowledge receipt of the SAE either via fax, e-mail or telephone. If the site has not received an acknowledgment within 24 hours, site are instructed to contact the LCTU to confirm receipt of the original SAE.

The TC/delegate must initial and date each SAE received. **Each SAE MUST be entered as they are received** onto the LCTU PV database (link below) in the order it is received per fax time and date to log the SAE in the system. The SAEs will be consecutively numbered on a per patient basis when entered onto the LCTU PV database (www.lctu.org.uk/macro/Login/DatabaseChoice.aspx).

3.2 Minimum Information

Upon receipt of a paper SAE, the TC/delegate should check the SAE for completeness of the minimal information required for the Clinical Coordinator (CC) to be able to perform their evaluation (see **Table 2**). The reporting site should be contacted immediately (by telephone / email) in the event that the minimum required information is missing and then every 24 hours thereafter until the required missing data is received.

Table 2. Minimum information required for CC evaluation	
Patient trial number and initials	Event name and description
Site number	Definition of serious
Trial Information (short title)	Investigators causality assessment between the event and intervention
Date of onset	Investigators signature*
*Investigator i.e. the consultant names on the 'signature list and delegation of responsibilities log' who is responsible for the patients care.	

In addition to checking for minimal information, the TC/delegate must also check the SAE to ensure that:

- Multiple events have not been reported on the same SAE form
- It meets the definition of serious
- The event is not exempt from reporting
- The current version of the SAE form has been used
- The form has been signed and dated by a person appropriate to do so as listed on the site delegation log

- The SAE has been submitted within 24 hours of the event onset and if not a reason has been provided.

Should any problems be identified, the TC/delegate must contact the site immediately to resolve the issues.

SAEs that have missing minimal information or have any other issues that prevent CC assessment MUST still be entered onto the LCTU PV database to log the SAE in the system.

3.3 SAE Review by Clinical Co-ordinator (CC)

SAE forms should be sent to the CC no **later than 10 calendar days after receipt of the SAE at the LCTU.** In the event that the minimum required information has not been obtained from site, the SAE form should still be sent to the CC according to the above timelines. However, the CC should be informed of what data is missing. The missing data should be forwarded to the CC for review as soon as it becomes available.

Once the minimum required information has been entered onto the LCTU PV database (or the deadline for forwarding the SAE to the CC has been reached – see above), the TC/delegate should log into (using MACRO log in details) the assessment request system (link below) and select the SAE and a CC to assess the SAE.

https://www.lctu.org.uk/pharmacovigilance_Live/login.aspx?apptype=RequestAssessment

This will create an email notifying the CC that they have an SAE to review and assess. In the event of a failure with the LCTU PV database, the TC/delegate should fax the SAE form to the designated CC, together with a CC SAE Review Form **(Appendix 2)** ensuring the first part is completed before faxing.

The CC should log into the CC SAE Assessment Database and assess the SAE for seriousness, expectedness and causality using the CC SAE website guidelines provided by the trial team.

The CC is unblinded and will therefore know which arm the patient has been randomised to when making their assessment.

Causality should be assigned to the following:

1. Anaesthetic
2. Generality of surgery (including surgical airway, primary tumour resection)
3. Neck dissection surgery
4. Use of ARTISS fibrin sealant

Expectedness will be assessed against the following:

1. Neck dissection surgery
2. Use of ARTISS fibrin sealant

The CC should always answer yes/no as to whether the event was expected regardless of whether a causal relationship has been identified.

Once the CC has completed their assessment, a final notification email will be sent to the LCTU trial team confirming the outcome of the review. Note that if the local PI believes there is a causal relationship between the SAE and the intervention, and the event was not expected as per the protocol, the CC cannot over-rule the PI's assessment of causality and the SAE must be reported to REC.

The TC/delegate should download a copy of the final SAE report from the Report Manager (Pharmacovigilance>Serious Adverse Events>Live Reports>Individual Report) as a PDF file and save in the safety folder within the eTMF. A new folder should be created for each SAE received as patient number and SAE number (e.g. 046-0001-1). Within this a subfolder should be created for the type of report (e.g. Initial) and the file saved as per the folder name and type of report (e.g. 046-0001-1-initial). The original paper SAE form along with a copy of the PDF SAE report should also be filed in the DEFeND Safety Folder. An SAE adhesive label should be completed and placed on the front of the punched pocket containing the SAE report. The SAE report containing CC assessment should also be uploaded to the sponsor section of the LCTU portal.

3.4 If the SAE does not require expedite reporting

No further action is required. The SAE should be reported to Sponsor as part of the 6 monthly line listings. The SAE should also be included in the line listings reported to the trial oversight committees.

3.5 If the SAE requires expedite reporting

If either the PI or the CI/CC reviews the SAE and decides that it is unexpected and related to the trial intervention (ARTISS fibrin sealant and/or neck dissection) then the SAE requires expedited reporting to REC. The event will be assigned the next consecutive Expedited SAE number by the TC/delegate and this will be documented on the SAE adhesive label on the front of the punched pocket containing the SAE report.

The date the SAE was reported to the LCTU is used as the start (Day 0) for reporting timeframes. The Expedited SAE number assigned must be transcribed onto all follow-up forms received, in addition to any other paperwork received concerning the event (the SAE number should also be provided on each piece of paperwork relating to the event).

The Expedited SAE must then be reported to REC within 15 days after receiving the SAE at the LCTU.

Reporting to REC:

It is the responsibility of the TC to report the SAE requiring expedited reporting to REC. The Report of Serious Adverse Events for non-CTIMPS should be downloaded from the HRA website using the link below and completed with guidance from the CI before being signed off by the CI. This along with a copy of the SAE Report should be emailed to REC within 15 days of being notified of the SAE. The REC for DEFeND is Greater Manchester East (nrescommittee.northwest-gmeast@nhs.net).

http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

The REC co-ordinator should acknowledge the receipt of all safety reports within 30 days by signing and returning the safety report form.

Informing Sponsor:

At the time of reporting to REC, the TC/delegate must also upload a copy of the HRA Report of Serious Adverse Events for non-CTIMPs to the sponsor area of the portal alongside the SAE report.

Informing local PIs:

The TC will inform the local PIs of all participating DEFeND sites of all SAEs requiring expedited reporting. This will be done in the form of a blinded line listing which will be sent on a 6 monthly basis via email. The PIs will be requested to reply to the email by way of receipt. The TC will file a copy of the blinded line listing in the DEFeND Safety Folder.

The details of expedited reporting to all relevant parties should be documented on the LCTU Expedited SAE Report Checklist for non-CTIMPS TM031_CHK1. Copies of the submission documentation sent to REC and Sponsor including any correspondence and the completed Expedited SAE Report Checklist should be filed in the relevant SAE folder within the DEFeND Safety Folder and eTMF along with the initial / follow up SAE form. Email correspondence should also be filed.

The LCTU SUSAR tracker must also be updated after the expedited SAE has been submitted to REC to track who submitted the report and when. SAEs in progress will be followed up on a weekly basis by senior TCs to ensure that reporting deadlines are met.

3.6 Follow-up Data

The TC/delegate must periodically request SAE follow-up reports from sites for any events stated as 'not resolved/ongoing' on the initial report. The site should provide SAE follow-up data as soon as it becomes available. Sites should report follow-up data by updating the original SAE form and marking it 'follow-up'.

When follow up information is received at the LCTU:

- The information should be entered onto the PV database as soon as it is received.
- The 'SAE Type' field should be updated every time follow up information is received (e.g. initial changed to follow up 1, 2, 3 etc.)
- The date notified should be changed every time follow up information is received.

Updates to the following fields will trigger re-assessment by the local investigator and CC:

- Outcome changed to FATAL (i.e. caused death)
- Overall diagnosis
- Signs and symptoms
- Relevant medical history
- A worsening of or a new test result
- Causality assessment

If the follow-up data requires re-assessment by the CC, the same steps and timelines for processing an initial report as detailed in section 3.3 should be followed. All updated information, whether or not it requires reassessment by the CC should be reported to REC within 15 days of receiving the updated information. In addition, the TC/delegate should download the 'Individual Report (with changes)', which highlights the updates made from the initial report, from Report Manager. This should be saved as a PDF in the corresponding SAE folder within the safety section of the eTMF. A sub folder for the follow up should be created e.g. 'follow up 1' and saved as patient number, SAE number followed by highlighted changes (e.g. 046-0001-1_highlightedchanges). A copy of this PDF report should be emailed to the CC to aid them with their reassessment.

It should be noted that a follow-up SAE may require expedited reporting even if the initial report did not as not all information may have been available when the SAE was initially reported. In such a case the reporting timelines detailed in section 3.5 will apply to when the follow-up report was received.

When a Notice of Death form is received at the LCTU, the TC or delegated individual must cross check this against any associated/ongoing SAEs for consistency:

1. Overall diagnosis (if grade 5, overall diagnosis and reason for death on the notice of death form should correspond).
2. Outcome:

a. If the outcome is fatal the overall diagnosis of the SAE must correspond with the reason for death given on the Notice of Death form.
b. Any other SAEs, unrelated to the cause of death that were ongoing should have 'ongoing at death' as the outcome.
c. Date of death should be detailed as the end date on any SAEs that were ongoing at death.

3. Any inconsistencies noted should be queried with site and updates requested

4. Clinical Co-ordinators

A list of CCs authorised to assess SAEs are listed on the trial specific delegation log. Contact details for all CC's can be found in the relevant section of the trial safety folder.

CCs should inform the TC of any absence which the TC will record in the trial safety folder. This should be referred to when assigning SAEs for review.

5. Informing the sponsor/other external parties

The TC/delegate will email line listings of all Serious Adverse Events reported on the study every 6 months in accordance with the Internal Delegation Plan. Sponsor will have access to individual SAE reports and HRA Reports of Serious Adverse Events (for expedited events) via the Portal.

The sponsor will have read-only access to the LCTU PV database which will allow them to see and print all SAEs reported.

6. Pregnancy reporting

Pregnancy is listed as an exclusion criterion for entry to the DEFeND trial.

In the event of a patient becoming pregnant after recruitment to the trial, this fact should be reported in the same way as an SAE (section 3.1) using the Pregnancy Form **(Appendix 3)**. The guiding principles in this event are:-

i) If the patient has not yet received treatment, or completed treatment, the patient may be withdrawn from the trial.
ii) Once treatment is complete, i.e. the patient is in follow-up phase, it may well be possible to retain the patient to the conclusion of the trial.
iii) A decision will be made in the best interests of the patient between the treating clinician and the CI as to retention in the trial and any continuing cancer therapy.

7. Pharmacovigilance / Safety Process – Testing Plan

Two 'Dummy SAEs' will be created per CC using a clearly marked, 'Dummy' SAE form. These SAEs will be entered onto the PV system by the TC and assigned to the CC to review. These dummy SAEs will be fully assessed by the Chief Investigator (CI) and TC to check for any deviations from the procedure and any discrepancies in the assessments made.

Once the review has been performed, a DEFeND Clinical Coordinator SAE Process Review Check Form will be completed by the TC.

Once the testing is complete, a review of the shortcomings of the process and actions required will be done by the CI and TC and this plan amended if required. The CC will be asked to feed back on the process and let the trial team know of any changes they wish to make. All documentation for testing is filed in the TMF.

7.1 Holiday Cover

LCTU Trial Staff:
Holiday cover for LCTU trial staff will be managed centrally through the LCTU Operational Director / Deputy Operational Director.

Clinical Coordinators:
The CCs should contact the TC/delegate with any dates that they are unavailable to review SAEs (i.e. on annual leave, away at conferences). If there are any dates where the CI and CC are unavailable, the TC/delegate must liaise with the CI/CC to ensure that SAE review is covered.

Approval of the DEFeND Safety Plan

The DEFeND Safety Plan (Version: 1 Date: 27/06/2018) has been agreed and approved by the following personnel:

Name: SEEMA CHAUHAN **LCTU Operational Director / Deputy Operational Director**

Signature: S Chauhan Date: 14/09/2018.

Name: Richard Scotson **Trial Statistician**

Signature: Date: 14/09/2018

Name: ANDREW SCHACHE **Chief Investigator**

Signature: Date: 18/9/18

Name: MANDEEP BAJWA **Trial Coordinator**

Signature: Date: 18/09/18

Name: JAMES A. McCANN **Clinical Coordinator**

Signature: Date: 10/10/18

Name: PAULA GILHANEY **Clinical Coordinator**

Signature: [signature] Date: 28/9/18

Appendix 1: Example of Trial SAE Form

ANY FIELD LEFT BLANK WILL BE DATA QUERIED BY THE LCTU

Version: 3 Date: 04/01/2018

LCTU Trials
Serious Adverse Event Form (Page 1)

DEFeND TRIAL NUMBER | PATIENT INITIALS

All follow-up information MUST be added to THIS form.

Please complete an adverse event form for each SERIOUS Adverse Event (SAE) that the subject experiences

Site No.: _ _ _ Principal Investigator: _____

Date initial report sent to Liverpool Cancer Trials Unit: _ _ / _ _ _ / _ _ _ _ *(dd/mon/yyyy)*

Reason SAE not reported within 24 hours of becoming aware:

☐ N/A
☐ Patient admitted to other hospital (not enough information to report)
☐ Other Specify: _____

☐ Initial Report ☐ Follow-up Report

SAE No.
(LCTU Stamp)

Section A: PATIENT INFORMATION

Sex: ☐ Male ☐ Female

Date of Birth: _ _ / _ _ _ / _ _ _ _

Days since surgery: _ _

Arm: ☐ ARTISS ☐ Standard of Care ☐ Not assigned

Section B: SERIOUS ADVERSE EVENT INFORMATION

Date of Onset: _ _ / _ _ _ / _ _ _ _ Date of Offset (if resolved): _ _ / _ _ _ / _ _ _ _

Outcome: ☐ Resolved ☐ Resolved with sequelae ☐ Not resolved/Ongoing
☐ Ongoing at death ☐ Fatal (i.e. caused death) ☐ Lost to follow-up

SAE Overall Diagnosis:

Signs and Symptoms of Serious Adverse Event	CTCAE v4 Grade (1-5)

Relevant medical history or concurrent medical conditions: _____

Relevant test results/lab data: _____

PRINCIPAL INVESTIGATOR: PRINT NAME: _____

SIGNED: _____ **DATE:** _ _ / _ _ _ / _ _ _ _

ANY FIELD LEFT BLANK WILL BE DATA QUERIED BY THE LCTU

Version: 3 Date: 04/01/2018

LCTU Trials
Serious Adverse Event Form (Page 2)

DEFeND TRIAL NUMBER | PATIENT INITIALS

Section C: CHANGE IN DRUG/TREATMENT—Not Applicable

Section D: SERIOUS CRITERIA

DEFINITION OF 'SERIOUS' - TICK ALL THAT APPLY

☐ Subject died: → Date of Death: __ __/__ __ __/__ __ __ __

☐ Involved or prolonged hospitalisation: → Date of admission: __ __/__ __ __/__ __ __ __
→ Date of discharge: __ __/__ __ __/__ __ __ __

☐ Involved permanent or significant disability or incapacity

☐ Life threatening

☐ Congenital anomaly

☐ Other: please specify: _____

_____

Is this an Adverse Event of Special Interest ? ☐ No ☐ Yes

Section F: CAUSALITY (To be completed by Investigator)

In your opinion was the adverse event related to:	No	Unlikely	Possibly	Probably	Highly Probable	SmPC Checked
Subject's original condition / other illness						
Anaesthetic						
Generality of Surgery (e.g. surgical airway, tumour resection)						
Neck Dissection						
ARTISS fibrin sealant						Yes / No

Section G: ADDITIONAL INFORMATION (To be completed by Investigator)

Is this an interaction with ARTISS fibrin sealant? ☐ No ☐ Yes

If yes please provide details: _____

PRINCIPAL INVESTIGATOR: PRINT NAME: _____

SIGNED: _____ **DATE:** __ __/__ __ __/__ __ __ __

ANY FIELD LEFT BLANK WILL BE DATA QUERIED BY THE LCTU

LCTU Trials
Serious Adverse Event Form (Page 3)

Version: 3, Date: 04/01/2018

DEFeND

TRIAL NUMBER

PATIENT INITIALS

All follow-up information on drug causality MUST be added to THIS form. Please write in CAPITAL letters.

Section E: CONCURRENT DRUG INFORMATION (To be completed by Investigator)

No	Drug	Causality	Route (IV, PO, etc)	Dose & Units (or infusion rate, if IV)	Frequency (od, pm, per protocol, etc)	Date (dd/mon/yyyy)		Indication	Treatment Overdose
						Started	Stopped If continuing enter 'Cont'		
1		☐ No ☐ Unlikely ☐ Possibly ☐ Probable ☐ Highly Probable				__/___/____	__/___/____		Yes / No
2		☐ No ☐ Unlikely ☐ Possibly ☐ Probable ☐ Highly Probable				__/___/____	__/___/____		Yes / No
3		☐ No ☐ Unlikely ☐ Possibly ☐ Probable ☐ Highly Probable				__/___/____	__/___/____		Yes / No
4		☐ No ☐ Unlikely ☐ Possibly ☐ Probable ☐ Highly Probable				__/___/____	__/___/____		Yes / No

Please fax all 3 completed pages to the Liverpool Cancer Trials Unit on +44 (0) 151 794 8930 / 8931 / 8247

PI: PRINT NAME: _____ **SIGNED:** _____ **DATE:** __ __ / __ __ __ / __ __ __ __

Appendix 2: Example of Trial SAE Review Cover Sheet

Liverpool Cancer Trials Unit
University of Liverpool
First Floor, Block C
Waterhouse Building
3 Brownlow Street
Liverpool, L69 3GL

FAX MESSAGE

To: Fax: Location: **DEFeND SAE REPORT** ***URGENT*** Phone ❑ Email ❑ Fax ❑	From: DEFeND Trial Team Date: Pages: Telephone: Fax: Email:

Dear Clinical Co-ordinator,

DEFeND SAE for review

Please find attached an SAE that has been reported to the LCTU for the DEFeND trial.

The SAE began:

Date: ___ / ___ / ___

___ days after surgery

I would be grateful if you could review this SAE and return the completed table (see overleaf) either by fax or email to LCTU within 48 hours.

Yours sincerely,

Mandeep Bajwa
NIHR Doctoral Research Fellow / DEFeND Trial Co-ordinator

Subject Trial Number	Subject Initials	SAE Number	Severity of Event	Relatedness	Expected	SUSAR
			❑ Subject died ❑ Involved or prolonged hospitalisation ❑ Involved permanent or significant disability or incapacity ❑ Life threatening ❑ Congenital ❑ Other (specify)	❑ None ❑ Unlikely ❑ Possible ❑ Probable ❑ Highly probable	❑ Yes ❑ No	❑ Yes ❑ No

Print name: _____ **Signature:** _____

Date: ___ / ___ / ___

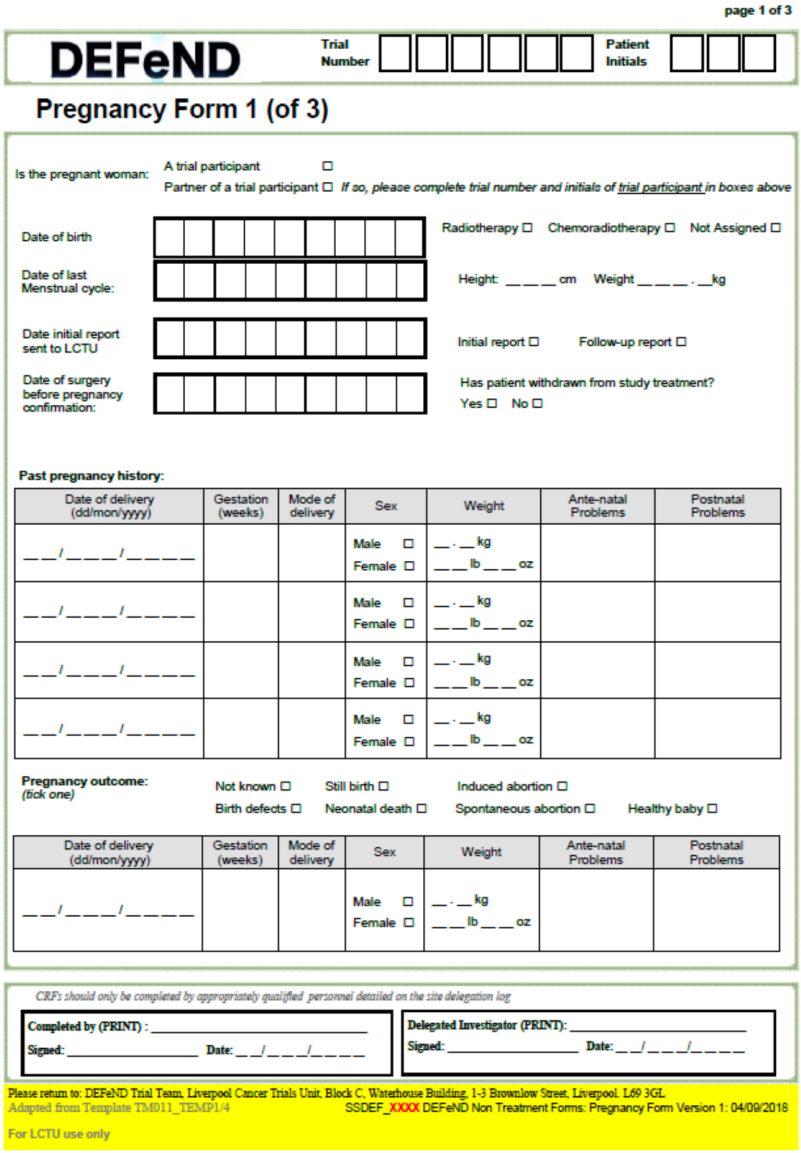
N.B. Information contained in this message is intended only for the person to whom it is addressed. It may be privileged and confidential and its disclosure may be prohibited by law. Please inform us immediately if you receive this message in error.

Sent by:

Date sent:

Time sent:

Appendix 3: Example of Trial Pregnancy Report Form



page 1 of 3

DEFeND Trial Number ☐☐☐☐☐☐ Patient Initials ☐☐☐

Pregnancy Form 1 (of 3)

Is the pregnant woman: A trial participant ☐
Partner of a trial participant ☐ *If so, please complete trial number and initials of trial participant in boxes above*

Date of birth ☐☐☐☐☐☐☐☐ Radiotherapy ☐ Chemoradiotherapy ☐ Not Assigned ☐

Date of last Menstrual cycle: ☐☐☐☐☐☐☐☐ Height: ____ cm Weight ___ . __kg

Date initial report sent to LCTU ☐☐☐☐☐☐☐☐ Initial report ☐ Follow-up report ☐

Date of surgery before pregnancy confirmation: ☐☐☐☐☐☐☐☐ Has patient withdrawn from study treatment? Yes ☐ No ☐

Past pregnancy history:

Date of delivery (dd/mon/yyyy)	Gestation (weeks)	Mode of delivery	Sex	Weight	Ante-natal Problems	Postnatal Problems
__/___/____			Male ☐ Female ☐	__.__kg __lb__oz		
__/___/____			Male ☐ Female ☐	__.__kg __lb__oz		
__/___/____			Male ☐ Female ☐	__.__kg __lb__oz		
__/___/____			Male ☐ Female ☐	__.__kg __lb__oz		

Pregnancy outcome: *(tick one)*
Not known ☐ Still birth ☐ Induced abortion ☐
Birth defects ☐ Neonatal death ☐ Spontaneous abortion ☐ Healthy baby ☐

Date of delivery (dd/mon/yyyy)	Gestation (weeks)	Mode of delivery	Sex	Weight	Ante-natal Problems	Postnatal Problems
__/___/____			Male ☐ Female ☐	__.__kg __lb__oz		

CRFs should only be completed by appropriately qualified personnel detailed on the site delegation log

Completed by (PRINT) : _____
Signed: _____ **Date:** __/___/____

Delegated Investigator (PRINT): _____
Signed: _____ **Date:** __/___/____

Please return to: DEFeND Trial Team, Liverpool Cancer Trials Unit, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool. L69 3GL
Adapted from Template TM011_TEMP1/4 SSDEF_XXXX DEFeND Non Treatment Forms: Pregnancy Form Version 1: 04/09/2018

For LCTU use only

DEFeND Trial Number ☐☐☐☐☐☐ Patient Initials ☐☐☐

Pregnancy Form 2 (of 3)

If adverse pregnancy outcome occurred, please indicate relationship to study treatment

Relationship	Anaesthetic	Generality of Surgery	Neck Dissection	ARTISS
None	☐	☐	☐	☐
Unlikely	☐	☐	☐	☐
Possible	☐	☐	☐	☐
Probable	☐	☐	☐	☐
Highly Probable	☐	☐	☐	☐

CRFs should only be completed by appropriately qualified personnel detailed on the site delegation log

Completed by (PRINT) : _____
Signed: _____ **Date:** __/___/____

Delegated Investigator (PRINT): _____
Signed: _____ **Date:** __/___/____

Please return to: DEFeND Trial Team, Liverpool Cancer Trials Unit, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool. L69 3GL
Adapted from Template TM011_TEMP1/4 SSDEF_XXXX DEFeND Non Treatment Forms: Pregnancy Form Version 1: 04/09/2018

For LCTU use only

Pregnancy Form 3 (of 3)

DEFeND **Trial Number** ☐☐☐☐☐☐ **Patient Initials** ☐☐☐

Concurrent drug information:

Route codes:

1.Per oral	2.Intravenous	3.Intramuscularly	4.Subcutaneous	5.Rectal
6.Topical	7.Eye/ear	8.Nasal	9.Inhalation	10.Other (specify)_____

No	Brand Name / Therapy	Route (use codes 1-10 above)	Dose & Units	Frequency	Start Date (dd/mon/yyyy)	End Date (dd/mon/yyyy)	Disease Indication
1					__/___/____	__/___/____	
2					__/___/____	__/___/____	
3					__/___/____	__/___/____	
4					__/___/____	__/___/____	
5					__/___/____	__/___/____	
6					__/___/____	__/___/____	
7					__/___/____	__/___/____	
8					__/___/____	__/___/____	
9					__/___/____	__/___/____	
10					__/___/____	__/___/____	
11					__/___/____	__/___/____	
12					__/___/____	__/___/____	
13					__/___/____	__/___/____	
14					__/___/____	__/___/____	
15					__/___/____	__/___/____	
16					__/___/____	__/___/____	
17					__/___/____	__/___/____	
18					__/___/____	__/___/____	

CRFs should only be completed by appropriately qualified personnel detailed on the site delegation log

Completed by (PRINT): _____

Signed: _____ **Date:** __/___/____

FAX COMPLETED FORM TO THE LCTU: FAX +44 (0) 151 794 8931

Delegated Investigator (PRINT): _____

Signed: _____ **Date:** __/___/____

Please return to: DEFeND Trial team, Liverpool Cancer Trials Unit, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool. L69 3GL

Adapted from Template TM011_TEMP1/4

SSDEF_XXXX DEFeND Non Treatment Forms: Pregnancy Form Version 1: 04/09/2018

For LCTU use only

Date form received: __/___/____ Date form entered: __/___/____ Initials: __ QC Check #: __ QC Date: __/___/____

A.10 Randomisation Instructions

DEFeND Randomisation Instructions **IRAS: 234851**

Title of Research Project: ***Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial***
EudraCT Ref (if applicable): Not applicable
Chief Investigator: Andrew Schache
Sponsor(s): University of Liverpool
Sponsor(s) Reference Number(s): UoL001346
Funder name and ref (if applicable): NIHR DRF-2017-10-117
IMPs (if applicable) (Please list all) : Not applicable
***Please complete all sections, ensure all sections are signed off and store in the Trial Master File after completion**

1. PURPOSE

The purpose of this document is to describe the processes for randomising patients into the DEFeND trial. Members of site staff authorised to perform randomisations/registrations for this study are listed on the relevant DEFeND Site Staff delegation log stored in the Investigator Site File.

Members of LCTU staff authorised to perform randomisations/registrations for this study are listed on the DEFeND Trial Delegation Log.

2. Study Design

This study is designed as a multicentre randomised external pilot trial with two arms. Patients due to undergo neck dissection surgery for head and neck cancer will be randomised to either the interventional arm or the control arm on a 1:1 basis. Patients will be stratified according to site (hospital) only. The 2 UK centres recruiting to the study are Aintree University Hospital and the Queen Victoria Hospital. In the interventional arm patients will undergo a neck dissection and have Artiss fibrin sealant (Baxter Healthcare LTD) applied as part of wound closure. In the control arm patients will simply undergo a neck dissection and have their wound closed without Artiss (standard of care). The allocation will be revealed at a specific time point during surgery (point of wound closure). Both the patient and outcome assessors will be blinded to the allocation. The patient will be followed up for a period of 6 weeks post-operatively before exiting the study.

3. Method for Receiving Requests for Randomisation/Registration

Randomisation of patients to the DEFeND trial is done at site via MACRO v4 and TARDIS system. In case MACRO or TARDIS are not working at site randomisation/Registration of patient will be carried out by the TC or a trained member of the LCTU staff.

Prior to randomisation, the participant's screening details should be entered into the LCTU portal DEFeND Screening Log by delegated site staff. This will automatically generate a screening number. All patients screened as part of the trial will be assigned a unique sequential screening numbers. A confirmation email with these details will be sent to site staff.
Research Staff at site who are authorised to register patients will be given a unique username and password to access MACRO v4 database: https://www.lctu.org.uk/macro/Login/LoginForm.aspx

4. Checks for Randomisation and Consent Form

Sites must check the randomisation eCRF and consent forms for data completeness, accuracy and to ensure the current locally approved versions of documentation have been used. **The TARDIS system will not allow patients to be randomised until the eligibility criteria have been met and entered onto MACRO by a research nurse/investigator (who is named on the site delegation log as being responsible for this task) and electronically signed off by the PI.**

Consent forms must be uploaded to the LCTU portal within 48 hours of a patient signing the form. A member of the LCTU study team will review and ensure the correct version of the consent form has been used and that it has been signed and dated by a researcher named on the delegation log.

5. Randomisation Procedure

After entering the patient's details in the DEFeND screening log via the LCTU portal, site staff should log into the MACRO database: www.lctu.org.uk/MACRO and complete the following MACRO forms:

1. Screening
2. Eligibility Criteria
3. Baseline Data
4. NDII
5. PainVAS

Once these forms have been completed the research nurse/investigator can check that the "Pre-randomisation Checklist" in the "Randomisation Form" has been auto-filled. This will include:

1. The correct version of the consent form has been completed and uploaded
2. Two independent members of LCTU staff have electronically authorised the consent form as being valid
3. The PI has electronically authorised the eligibility criteria
4. Baseline patient questionnaires have been completed (NDII and Pain VAS)

Once the Pre-randomisation Checklist has been filled the research nurse/investigator may sign-off the checklist as being complete. **Only once the Pre-randomisation Checklist has been signed-off can the patient be randomised.**

Randomisation will take place via a web based tool called "Treatment Allocation Randomisation System" or TARDIS. The MACRO database will generate a patient specific link to TARDIS once the pre-randomisation checklist has been signed-off. Click on this link to enter TARDIS, once in TARDIS please follow the steps below:

1. *Select 'Randomise Patient', enter your username and password, select DEFeND from the drop down menu, the click 'Go'*
2. *Select the screening number and site name from the drop down menu.*

3. *Select 'Click to validate patient'. A notice will appear on the screen 'Patient is eligible' and the patient's initials and hospital site name will populate automatically. Tick the correct site number.*
4. *Select 'Randomise Patient'*
5. *A window will pop up asking you to confirm that you want to go ahead with the randomisation. Click 'OK' to continue*
6. *A notice will appear that the patient has been successfully randomised. The allocated treatment arm will NOT be displayed. An automated confirmation will be sent to the surgeon's email address containing a link to reveal the allocation.*
7. *On the day of surgery once the surgeon has completed the neck dissection and ready for wound closure, a delegated member of the surgical team should complete the "Surgery" form in the MACRO database.*
8. *Once the "Surgery" form has been completed the allocation should be revealed via the link in the automated email. The time and date that the allocation is revealed will be cross checked against the relevant MACRO entries in the "Surgery" form as well as source data.*
9. *When completing the operation note the surgeon simply transcribes "wound closure as per DEFeND trial allocation".*

6. Back-up Randomisation Procedure

If MACRO or TARDIS are not available at site please contact LCTU immediately so that the process can be completed centrally. Please note that randomisation can only be completed centrally if the "Pre-randomisation Checklist" is populated correctly on the MACRO database. If MACRO and TARDIS are not available at site or centrally the patient cannot be randomised until the fault has been rectified. **There are no paper back-up procedures for the DEFeND study**.

7. Randomisation Errors

If an error in the randomisation process is identified AFTER the site has been informed of the treatment allocation, determine which category this falls into:

1. Administrative error at LCTU

- Notify TC immediately.
- Do not correct randomisation details on the MACRO database.
- Do not re-randomise patient.
- Complete a deviation report with details of the error and file it in the Trial Master File (TMF).

2. Patient randomised with all details correct but clinician/nurse subsequently telephones LCTU to complain that they are not happy with the treatment allocation.

- Do not amend randomisation details on the MACRO database/backup randomisation schedule.
- Do not re-randomise patient.
- Do not make any changes to the MACRO database
- Notify TC immediately who should then contact site to reiterate the randomisation process and clarify they are happy with the trial design/randomisation process.
- Generate a file note and file it in the TMF.

3. Any randomisation error that occurs in relation to allocation of treatment should be notified to the TC and TS (or another statistician at the LCTU) immediately to discuss the appropriate process to follow.

Administrative errors identified BEFORE notifying a site of the randomisation can be amended if appropriate (discuss with the TC) by restarting the randomisation process

Signatures

M. BAJWA Trial Co-ordinator	Signature	Date 12/10/18
R. Sachdeva Trial Statistician	Signature	Date 12/10/2018
S. CHAUHAN LCTU Operational Director / Deputy Director	Signature	Date 12/10/2018.

A.11 Unblinding Instructions

Liverpool Cancer Trials Unit

DEFeND Unblinding Instruction

WORK INSTRUCTION INS_D120	Version: 1.0 Date: 10/09/2018	Page 1 of 3

1.0 PURPOSE

The purpose of this work instruction is to describe the process for unblinding a patient in the unlikely event the use of Artiss Fibrin Sealant (Baxter Healthcare LTD) needs to be known.

2.0 ASSOCIATED DOCUMENTS

SSDEF_PROTOCOL – DEFeND Protocol

3.0 RESPONSIBILITY

It is the responsibility of the investigator / co-investigator to:

a) Ensure the allocation is not revealed to the patient and other site research staff for the duration of the study.

b) Only unblind the allocation if it is completely necessary i.e. if the patient suffers a complication of treatment and revealing the allocation is helpful to their ongoing care.

c) If required, unblind a patient's allocation formally via the Treatment Allocation Randomisation System (TARDIS)

It is the responsibility of the LCTU to:

a)If required, unblind a patient's allocation via TARDIS at the request of an investigator (via telephone confirmation).

b)Ensure the person requesting unblinding has unblinding permissions and provides their four-digit pin code to confirm this.

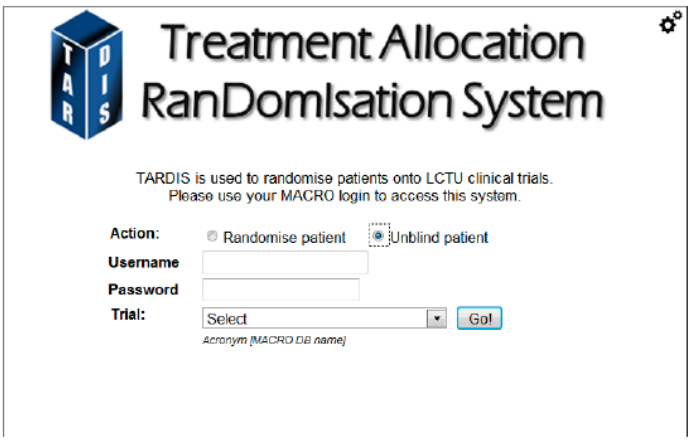
4.0 INSTRUCTIONS

The following steps should be followed in the event that unblinding a patient's allocation is necessary.

1. Go to www.lctu.org.uk/tardis.
2. On the Log in screen select 'unblind patient', enter your username and password, select 'DEFeND' from the trial drop down list and then select 'Go!'

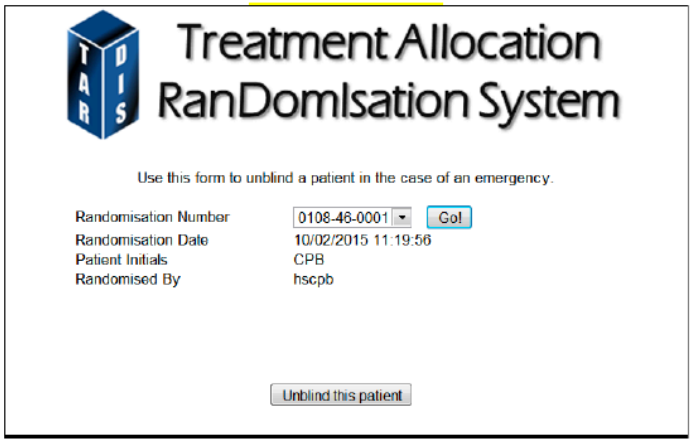
(adapted from template TM013_TEMP2/1)

LCTU only: enter the details of the investigator (name and four-digit passcode).



3. Select the patient's randomisation number from the drop-down list and select ***'Go!'*** to open the patient details.

4. If details are correct, proceed to unblind by selecting ***'Unblind this patient'***.



(adapted from template TM013_TEMP2/1)

5. An on-screen confirmation will appear confirming the allocation.

6. An automated email confirming unblinding will trigger to the investigator who performs (or requests) the unblinding and to the DEFeND trial team also.

Author Name (Print Name): MANDEEP BAZMA

Signature: _____ **Date:** 23/10/18

Approver (Print Name): ROB HANSON

Signature: _____ **Date:** 23/10/18

A.12 TSC Charter

Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

Trial Steering Committee (TSC) Charter

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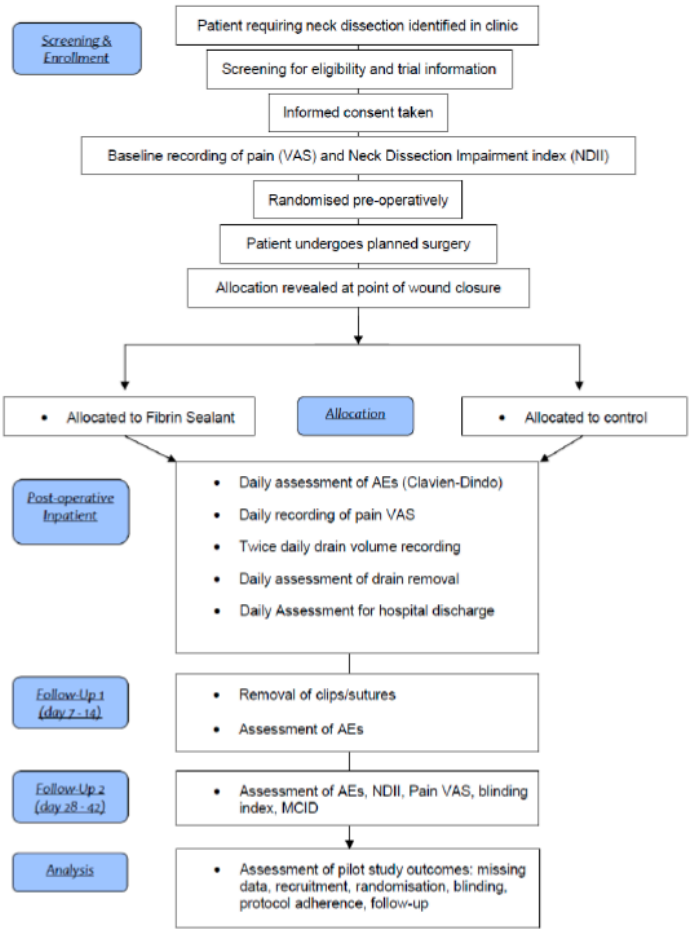
1. INTRODUCTION

1.1 Main Objectives of the Trial [1] and Trial Design

The key objectives of this randomised external pilot study are to assess the following points:

I. Whether patients can be recruited and retained at a rate of approximately 4 patients per month across the 2 centres.
II. Determining the effectiveness of the blinding strategy using blinding indices.
III. Ensuring the administrative processes of randomisation, allocation concealment and data management work well within the study.
IV. Assess adherence to the conditions of the protocol.
V. Provide evidence to inform the sample size calculation for the future phase III multicentre randomised trial.



[1] The term 'Trial' includes all clinical studies for in order to maintain consistent terminology

1.2 Scope of Trial Steering Committee (TSC) charter

This Trial Steering Committee (TSC) charter defines the roles and responsibilities of the TSC for the DEFeND study, and explains the TSC's relationship with other oversight committees and the Trial Management Group (TMG). This charter also describes the purpose and frequency of its meetings. Membership details of the TSC are provided in the TSC membership document TM040_TEMP4

2. ROLES AND RESPONSIBILITIES

2.1 General Responsibilities

The aim of the TSC is to provide overall independent supervision of the trial.

Collectively, the TSC members have the scientific, medical and clinical trial management experience to conduct and evaluate the trial and have joint oversight for the design, conduct and analysis of the clinical trial. The TSC should ensure that the trial is conducted to the standards set out in the ICH guidelines for Good Clinical Practice (GCP).

Please note that the DEFeND study does not require an Independent Safety and Data Monitoring Committee (DMC). Independent members of the TSC will undertake the roles of the DMC.

Such responsibilities include:

- Making major decisions such as continuing or terminating the trial
- Determine whether amendments to the protocol or changes in study conduct are required
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from external sources
- Considering recommendations from the Independent members of the TSC and any other oversight committee
- Advising the TMG on all aspects of the trial

It is necessary that the members of the TSC have no major concerns with the protocol, Draft versions will therefore be circulated in advance of the initial meeting to permit comments from individual members on their areas of expertise to be taken into account in the final draft. There will be a time limit to receive comments on each draft and it is important that any concerns are raised early to avoid changes being made at the initial meeting. Conversely if members have no concerns it is helpful to state this explicitly in reply to each circulated draft.

Representatives of the TMG that sit on the TSC have the following responsibilities:

- Schedule TSC meetings in accordance with this charter
- Distribute the agenda and TSC report prior to each TSC meeting
- Write the meetings minutes and facilitate review and oversight by the trial sponsor

2.2 Responsibilities of the TSC Chairperson

The TSC chairperson (or vice-chair, if the chairperson is absent) is expected to facilitate and summarise discussions; achieving consensus when possible.

When voting is required (see TM040_TEMP4 TSC Membership), it is preferable for the chairperson (or vice-chair) to give their opinion last.

When there are major trial issues raised by the TMG, the TSC chairperson (or vice-chair) should determine whether an unscheduled meeting should be held.

3. MEMBERSHIP OF THE TSC

3.1 TSC Members

Membership of the TSC is detailed in the TSC membership document TM040_TEMP4

3.2 Membership and Conflicts of Interest

TSC members must formally register their agreement to join the TSC by signing either the TSC Charter signature page, independent members (TM040_TEMP7) or the TSC Charter signature page, non-independent members (TM040_TEMP8) that they agree to be a member of the TSC and that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. TSC members must complete and return these forms no later than at the initial meeting.

Any observers (attendees who are not members) must sign a confidentiality agreement on the first occasion they attend a meeting (TM040_TEMP9).

3.3 Indemnity

The TSC membership has indemnity coverage via the University of Liverpool's Professional Indemnity insurance. This is in the event of the TSC being sued by a trial participant (or family member) for example.

4. Organisation of TSC meetings

4.1 Format of Meetings

TSC meetings will be arranged by the Trial Co-ordinator who will also prepare an agenda and TSC report (using the current LCTU template) and send to all members. These documents must be distributed no less than 5 working days prior to the TSC meeting, unless otherwise agreed with the TSC.

The Chief Investigator, Andrew Schache, should be available to attend all TSC meetings.

A suitable date should be arranged such that the members eligible to vote are present and decisions made where necessary (see section 7).

For any TSC members unable to attend the meeting, comments must be collated by the TMG via email.

TSC meetings will either be face-to-face or held via teleconference/video conference.

4.2 Initial TSC Meeting

At the first meeting, members will be provided with a copy of the clinical trial protocol, patient information sheets (PIS), Informed Consent Form (ICF), print out of the eCRF, and a copy of this TSC charter and membership document TM040_TEMP4.

The relevant signature pages must be completed prior to, or at the start of the initial meeting.

At the initial meeting the criteria for quorate will be defined and minuted, and the procedure for minute taking will also be confirmed.

4.3 Scheduled and Unscheduled TSC Meetings

The frequency of scheduled TSC meetings will be decided at the initial meeting (and noted in the minutes) but typically, the TSC will meet shortly after the ISDMC has met, so that the frequency will be determined by the frequency of scheduled ISDMC meetings. There may be periods when more frequent full meetings are necessary or rarely, when a meeting may be delayed more than a year (in either case the minutes should summarise the reasons for this).

Major trial issues may need to be dealt with between meetings, by phone or by email. TSC members should be prepared for such instances. The TSC chairperson (or vice-chair, in their absence) should decide whether an unscheduled meeting should be held and such meetings will be organised by the TMG (unless otherwise specified by the sponsor). These meetings must be minuted, with approval confirmed by email from the Committee Chair.

4.4 Final Study Meeting

The TSC will be expected to review the final statistical report. The expected timing of this is specified in the trial protocol and Statistical Analysis Plan (SAP).The final analysis may also be triggered if the TSC terminates the study early on the recommendation of the independent members. Depending on the publication policy specified in the protocol, the TSC may also be required to approve the Clinical Trial Report (CTR). This will be submitted up to one year after trial closure, hence the final meeting of the TSC may not occur until several months after trial closure, and it is at the discretion of the TSC to define when the final meeting will be.

5. DECISION MAKING

5.1 Achieving Consensus

Every effort should be made to achieve consensus between the TSC members and this should be facilitated by the chairperson (or, in their absence, the vice-chair). It is important that all potential implications are considered before a final decision is made.

If a consensus cannot be reached, the decision will be put to a vote.

5.2 Voting

Voting arrangements are detailed in section 2 of TM040_TEMP4

6. DOCUMENTATION OF TSC MEETINGS

6.1 Minutes of TSC meetings

Unless otherwise decided at the initial TSC meeting, a member of the TMG (typically the Trial Coordinator) will take minutes of the meetings. A summary of the main points discussed with a list of clearly marked action points should be sufficient.

All members of the TSC should review the meeting minutes. If no comments are returned within 15 working days of sending out the draft minutes, it will be assumed that the attendee has no comments and is happy with the draft minutes. Following the 15 working day period, the minutes should be finalised and sent to all attendees and non-attendees for information.

7. COMMUNICATION WITH THE TMG & SPONSOR

The TSC should ensure that appropriate efforts are made to ensure that relevant discussions are adequately disseminated by the TMG and that due consideration is given to how decisions will be implemented by the TMG.

Diagrams 1 and 2 below show the process for communication between the trial oversight committees and the sponsor.

Diagram 1:
Communication diagram for disseminating discussions from Trial Oversight Committee meetings

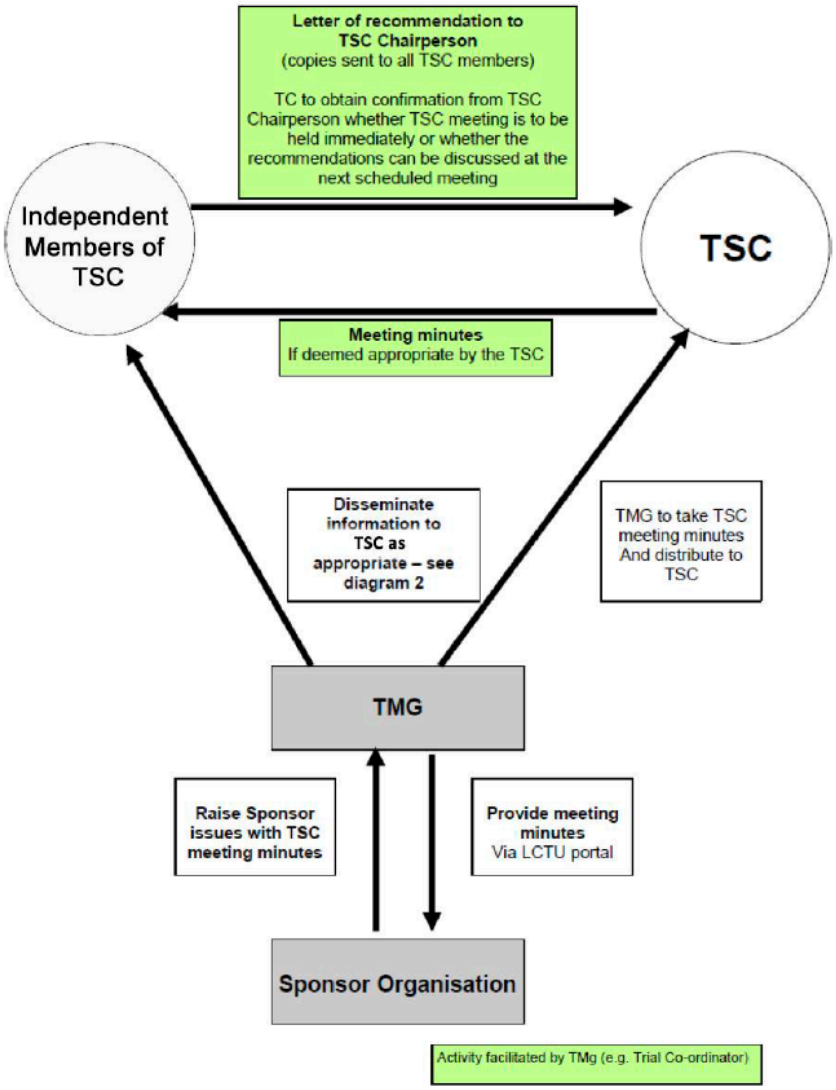
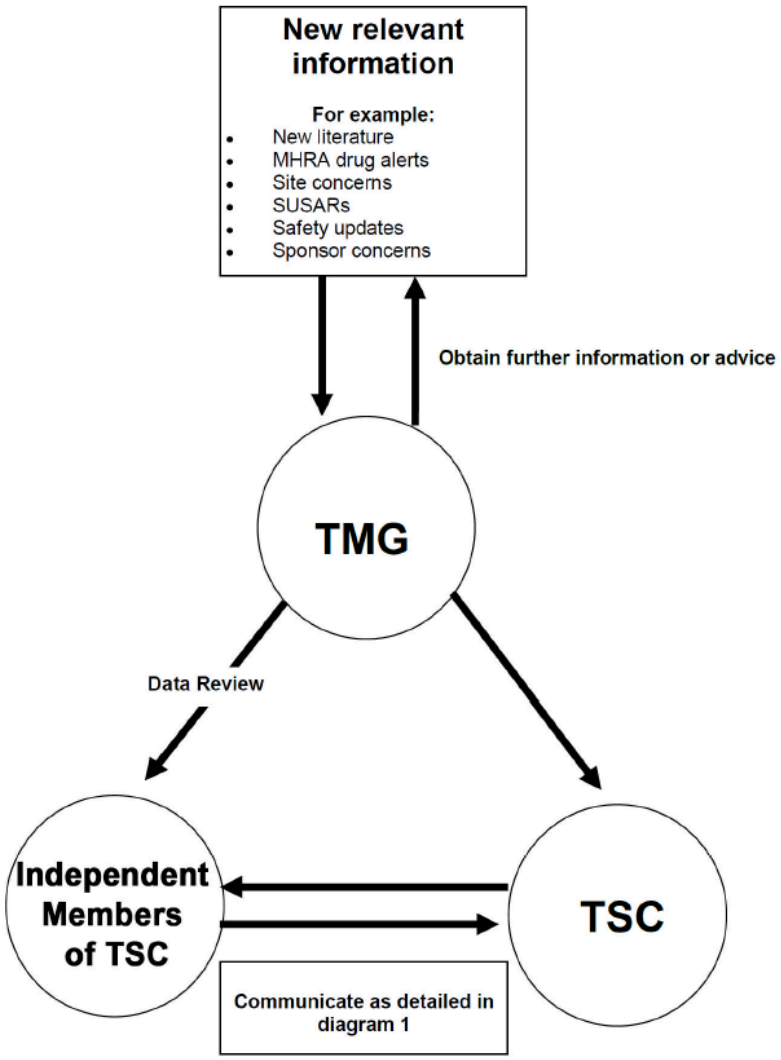


Diagram 2:
Communication diagram for disseminating new relevant information identified outside of Trial Oversight Committee meetings



7.1. Reporting to the Sponsor

The TMG shall provide final meeting minutes of all TSC discussions to the sponsor via the LCTU portal (see diagram 1).

If the sponsor raises any concerns with the TSC discussions, these will be relayed to the TSC via the TMG.

8. AFTER THE TRIAL

8.1. Publication of Results

The Chief Investigator has responsibility for ensuring that trial results will be published in a correct and timely manner. The TSC is the committee that should oversee this process.

If early release of (possibly provisional) trial results is being considered, the following points should be taken into account:

Origin of proposal to release early results

- Is the early release a result of a recommendation following a scheduled DMC meeting?
    - If "No", will the trial continue on to its planned final analysis?

Types of data

- Do the results refer to the primary endpoint or secondary endpoints?
- Is release only of recruitment or safety data?

Data quality

- Is patient accrual finished?
- Will all patients have had reasonable follow-up time (ie is trial maturity adequate)?
- Is extent of unresolved queries, outstanding data acceptable?
- Do the results depend on review by an end-point committee?

Effects on patients

- Are all patients off treatment-arm–specific therapy?
- Will patient care be modified (switching, withdrawal) once results made public?

CTU workload

- Will resolving queries and chasing outstanding CRFs impose an undue workload burden?

Statistical considerations

- Will power for the pre-planned primary endpoint still be reasonable (alternatively, will the precision of the estimated treatment effect be acceptable or will the confidence limits be able to exclude either benefit or harm?)
- Are statistical programs ready?
- Is the existing SAP appropriate/feasible with reduced follow-up?
    - If "No" is there a specific early analysis plan/wording in the SAP to cover early release ?

8.2. TSC approval of publications

The TSC members should be given at least 10 working days, and if possible 20 to read and comment on any draft publications that report outcome measures and/or details of the TSC. This may be done simultaneously to other groups reviewing the draft manuscript (e.g. ISDMC, trial investigators).

8.3. TSC constraints for divulging information

The TSC should not discuss confidential issues from their involvement in the trial until 12 months after the primary trial results have been published, unless permission is agreed within the TSC. They should not trade in stock of companies affected by the trial until the results are public knowledge.

Appendix B. ELECTRONIC CASE REPORT FORMS

B.1 Screening Form

DEFeND Screening Form

Patient Initials

NHS Number

Date of Birth (dd/mm/yyyy)

Gender
◎ Female
◎ Male

Screening Number

Hospital Site
◎ Aintree University Hospital
◎ Queen Victoria Hospital

Consultant Initials

Has a Patient Information Sheet (PIS) been provided? ◎ Yes ◎ No Version Number Date PIS handed to patient

Trial consent form signed? ◎ Yes ◎ No Version Number Date of consent to trial

***Consent form uploaded to PORTAL and auto email send to 'defend@liverpool.ac.uk' once above Q is YES**

B.2 Eligibility Form

DEFeND Eligibility Form

IMPORTANT: Only once this form has been completed and signed off by the PI may further data be entered for this patient.

INCLUSION CRITERIA

Is the patient due to undergo a lateral neck dissection?
◎ Yes
◎ No

Will the neck dissection include a minimum of 3 levels?
◎ Yes
◎ No

Does the patient have capacity to consent?
◎ Yes
◎ No

EXCLUSION CRITERIA

Is the patient under 18 years of age?
◎ Yes
◎ No

Is the patient undergoing a BILATERAL neck dissection?
◎ Yes
◎ No

Is the patient undergoing reconstruction with either a free or regional flap? (i.e. presence of vascular pedicle in the neck)
◎ Yes
◎ No

Is the patient a female of childbearing age?
◎ Yes
◎ No

Has a pregnancy test been performed?
◎ Yes
◎ No
◎ No, the patient declined because she is certain she is not pregnant
◎ No, the patient declined for other reasons

Is the patient either pregnant or breast feeding?
◎ Yes
◎ No, the pregnancy test was negative and the patient is not breast feeding
◎ No, the patient declined a pregnancy test but is certain she is not pregnant or breast f
◎ Uncertain

Does the patient have a known allergy to Aprotinin?
◎ Yes
◎ No

Has the patient undergone surgery in the last 6 months?
◎ Yes
◎ No

Was a fibrin sealant applied to the patient's wound during this operation?
◎ Yes
◎ No
◎ Uncertain

Does the patient have a known allergy to dairy products?
◎ Yes
◎ No

◎ **Patient has met the eligibility criteria**

Eligibility checklist completed by _____ Date completed _____

Generate email asking PI to sign-off

◎ PI click here to sign

PI's electronic signature _____ Date signed _____

B.3 Baseline Data Form

DEFeND Baseline Form

Site of primary tumour

If other site please specify

Histology (e.g. squamous cell carcinoma)

Has the patient had previous treatment/interventions to the neck?
- ◎ No previous treatment/intervention
- ◎ Previous IPSILATERAL radiotherapy (including chemoradiotherapy)
- ◎ Previous CONTRALATERAL radiotherapy (including chemoradiotherapy)
- ◎ Previous IPSILATERAL neck dissection
- ◎ Previous IPSILATERAL open biopsy (including sentinel lymph node biopsy)
- ◎ Both IPSILATERAL surgery and IPSILATERAL or CONTRALATERAL radiotherapy
- ◎ Other

If other treatment/intervention please specify

Height (m) Weight (kg) BMI

WHO Performance Status

Smoking
- ◎ Current
- ◎ Ex-smoker
- ◎ Never smoked

Number of years smoked Average number of cigarettes per day Pack Years

Average number of alcohol units consumed per week
- ◎ None
- ◎ Less than 14 units
- ◎ More than 14 units

Is there a history (or clinical suspicion) of alcohol abuse or dependence?
- ◎ Yes
- ◎ No

Diabetes
- ◎ Yes
- ◎ No

Is the patient on regular immunospressant medication? (e.g. steroids, Cyclosporine, Azathioprine, Tacrolimus)
- ◎ Yes
- ◎ No

Bleeding disorder (i.e. disease that results in excessive bleeding)
- ◎ Yes
- ◎ No

Is the patient on regular Antiplatelet medication? (e.g. Aspirin, Clopidogrel, Dipyridamole)
- ◎ Yes
- ◎ No

Is the patient on more than one Antiplatelet?
- ◎ Yes
- ◎ No

Is the patient on regular Anticoagulant Medication? (e.g. Warfarin, Apixaban, Dabigatran, Rivaroxaban)
- ◎ Yes
- ◎ No

Pre-operative Blood Results

Hb (g/l) (Male 130-180 Female 115-165)

Platelets (10^9/l) (140-400)

White Cell Count (10^9/l) (3.6-11.0)

PT - Prothrombin Time (s) (10-14)

B.4 Neck Dissection Impairment Index (NDII) Form

DEFeND NECK DISSECTION IMPAIRMENT INDEX (NDII)

Q1. Are you bothered by neck or shoulder pain or discomfort?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q2. Are you bothered by neck or shoulder stiffness?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q3. Are you bothered by difficulty with self-care activities because of your neck or shoulder? (e.g. combing hair, dressing, bathing etc.)	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q4. Have you been limited in your ability to lift light objects because of your shoulder or neck?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q5. Have you been limited in your ability to left heavy objects because of your shoulder or neck?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q6. Have you been limited in your ability to reach above for objects because of your shoulder or neck? (e.g. from shelves, tables or counters)	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q7. Are you bothered by your overall activity level because of your shoulder or neck?	○ not at all ○ a little bit ○ a moderate amount ○ quite a lot ○ a lot
Q8. Has the treatment of your neck affected your participation in social activities?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q9. Have you been limited in your ability to do leisure or recreational activities because of your shoulder or neck?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot
Q10. Have you been limited in your ability to do work (including work at home) because of your shoulder or neck?	○ not at all ○ a little bit ○ a moderate amount ○ quite a bit ○ a lot

Raw NDII Score ☐

Standardised NDII Score ☐

B.5 Neck Pain Scale Form

Study: DEFeND (Version: 1) Form: PainVAS Page 1 Printed 2018/10/03 10:23:18

DEFeND NECK PAIN SCALE

Pain score (out of 10) ☐

B.6 Randomisation Form

DEFeND Randomisation Form

PRE-RANDOMISATION CHECKLIST

Trial consent form uploaded? Version Number Date of consent to trial

◎ Click here to sign-off first consent authorisation

First central electronic signature Date of first authorisation

◎ Click here to sign-off second consent authorisation

Second central electronic signature Date of second authorisation

Eligibility criteria signed off by PI?

Baseline NDII completed?

Baseline Neck Pain Scale completed?

◎ Please click here to sign-off pre-randomisation checklist

Once pre-randomisation sign-off completed then patient specific link to tardis created to randomise patient.
Once patient randomised, automated tick box confirms randomisation.
Importantly TARDIS does not reveal the allocation to MACRO.

◎ The patient has been randomised successfully

***After rand, emails for chosen surgon(s) receive email for revealing allocation.**
Email has link to TARDIS to reveal allocation (just for that patient).
Allocation revealed on screen and following written to MACRO:
Who revealed, time/date revealed

B.7 Day of Surgery Paper Case Report Form

DEFeND Day of Surgery Form

Please complete this form before the patient leaves recovery. Please file this form in the front of the case notes.

Patient screening number ☐☐☐ – ☐☐☐☐ **Patient initials** ☐☐☐

Date of surgery D D M M M Y Y Y Y

ASA (please tick) I ☐ II ☐ III ☐ IV ☐ V ☐ VI ☐

Concurrent Mucosal Resection (Please tick) Yes ☐ No ☐

Start time of Neck Dissection i.e. knife to skin (24hr clock) H H : M M

Neck Levels Dissected (please tick a minimum of 3) I ☐ II ☐ III ☐ IV ☐ V ☐ VI ☐

Cutting instrument used for >50% of dissection (please tick)

- ☐ Cold Steel
- ☐ Cutting Diathermy
- ☐ Harmonic Scalpel
- ☐ Ligasure
- ☐ Other (specify) .....

Estimated Blood Loss ☐☐☐☐ ml

Time when ready for wound closure (24hr clock) H H : M M

Names & grade of surgeons present in theatre at point of allocation reveal (include juniors)

Please continue to page 2

DEFeND Day of Surgery Form

Please complete this form before the patient leaves recovery. Please file this form in the front of the case notes.

Patient screening number ☐☐☐ – ☐☐☐☐ **Patient initials** ☐☐☐

Was allocation revealed successfully? Yes ☐ No ☐

If the allocation was NOT revealed successfully please use this space to briefly explain why

Theatre Staff Sign-off. To be signed when patient leaves theatre

Completed by: Occupation:

Signature Date: D D M M M Y Y Y Y

Time patient left theatre recovery (24hr clock) H H : M M

Recovery Staff Sign-off. To be signed when patient leaves recovery

Completed by: Occupation:

Signature Date: D D M M M Y Y Y Y

Time drain emptied on night of surgery H H : M M **Please tick this box if drain not emptied** ☐

Exact volume in drain using measuring cylinder ☐☐☐☐ **ml**

Ward Night Staff Sign-off. To be signed by Night Staff once drain emptied and measured

Completed by: Occupation:

Signature Date: D D M M M Y Y Y Y

B.8 Day of Surgery Electronic Case Report Form

DEFeND Surgery Form

Date of Surgery (dd/mm/yyyy)

ASA
- I - A normal healthy patient
- II - A patient with mild systemic disease
- III - A patient with severe systemic disease
- IV - A patient with severe systemic disease that is a constant threat to life
- V - A moribund patient who is not expected to survive without the operation
- VI - A patient who is declared brain dead and is having their organs harvested

Start time of surgery i.e. knife to skin (24hr clock, hh:mm)

Is the patient undergoing a concurrent mucosal resection?
- Yes
- No

Neck levels dissected, click all that apply
- Level I
- Level II
- Level III
- Level IV
- Level V
- Level VI

Number of neck levels dissected

What cutting instrument was used to carryout the majority (>50%) of the dissection?
- Cold steel (either scalpel or scissors)
- Cutting diathermy (finger switch)
- Harmonic scalpel
- LigaSure
- Other

If other please specify

Estimated blood loss (ml)

Time when ready for wound closure (24hr clock, hh:mm)

Surgeons present in theatre

Name	Grade

We will need to keep the list of names updated along with the names in LCTU portal. Presumably we can't extract names from the portal? Also we can put the grade of surgeon down with the name making the grade box superfluous

List of all consultants (>30) any of who can be selected per patient. Email addresses are auto completed based on managed lists via Helpdesk job.

Extract data from TARDIS/bespoke web page stating whether allocation revealed also the time date and who. Once the allocation has been revealed once it is not accessible again. TARDIS does NOT tell MACRO what the allocation is.

Allocation revealed?
- Yes
- No

Reveal Date

***These are auto-populated**

Time patient left recovery (24hr clock, hh:mm)

B.9 Post-operative Complication Form

DEFeND **Post-Operative Complication Form**

ASSESSMENT OF POST-OPERATIVE COMPLICATIONS

Has the patient experienced any complications as a result of their recent surgery?
- ◎ Yes
- ◎ No

Please record the name of the clinician making assessment for complications

Please record the grade of clinician making assessment for complications
- ◎ Consultant
- ◎ Specialty Trainee (or medically qualified equivalent)

Has the patient experienced a neck wound infection?
- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the neck wound infection
- ◎ Localised and superficial to platysma e.g. stitch abscess
- ◎ Spreading cellulitis or superficial wound infection with no underlying collection treated with antibiotics
- ◎ Collection deep to platysma requiring drainage without GA
- ◎ Collection deep to platysma requiring drainage under GA
- ◎ Collection with life threatening sequelae (e.g. airway obstruction, severe sepsis, septic shock) - Single organ dysfunction
- ◎ Collection with life threatening sequelae (e.g. airway obstruction, severe sepsis, septic shock) - Multiorgan dysfunction
- ◎ Patient death

Has the patient experienced another surgical site infection (other than neck wound)?
- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the surgical site infection
- ◎ Localised and superficial infection requiring topical or non-invasive treatment
- ◎ Infection requiring treatment with antibiotics only
- ◎ Collection requiring drainage without GA
- ◎ Collection requiring drainage under GA
- ◎ Collection with life threatening sequelae (e.g. airway obstruction, severe sepsis, septic shock) - Single organ dysfunction
- ◎ Collection with life threatening sequelae (e.g. airway obstruction, severe sepsis, septic shock) - Multiorgan dysfunction
- ◎ Patient death

Has the patient experienced a haematoma or bleeding?
- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the haematoma or bleeding
- ◎ Haematoma not requiring drainage or suitable for simple aspiration with needle (not radiologically guided)
- ◎ Post-operative bleeding requiring blood transfusion
- ◎ Haematoma requiring drainage without GA (includes radiologically guided aspiration/drainage)
- ◎ Haematoma requiring drainage or return to theatre for haemostasis
- ◎ Life threatening haematoma or bleeding sufficient to cause airway obstruction or hypovolaemic shock - Single organ dysfunction
- ◎ Life threatening haematoma or bleeding sufficient to cause airway obstruction or hypovolaemic shock - Multiorgan dysfunction
- ◎ Patient Death

Has the patient experienced any neck wound breakdown or fistula?
- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the wound breakdown or fistula
- ◎ Superficial skin dehiscence (platysma layer intact) managed with simple dressings
- ◎ Small fistula maaged by an enteral tube or parenteral nutrition only
- ◎ Deep dehiscence (through platysma layer) or fistula managed with an invasive procedure without GA
- ◎ Deep dehiscence (through platysma layer) or fistula managed with an invasive procedure under GA
- ◎ Evidence of single organ dysfunction
- ◎ Evidence of multiorgan dysfunction
- ◎ Patient death

Has the patient experienced a post-operative chyle leak?
- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the chyle leak

- ◎ Low output leak (<500ml/24hrs) suitable for low fat diet and compression only
- ◎ Requirement for pharmacological management including Total Parenteral Nutrition
- ◎ Managed with radiologically guided occlusion without GA
- ◎ Managed with a procedure under GA
- ◎ Evidence of single organ dysfunction
- ◎ Evidence of multiorgan dysfunction
- ◎ Patient death

Has the patient experienced a seroma or sialocele?

- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the seroma or sialocele

- ◎ Small collection not requiring drainage or suitable for needle aspiration (not radiologically guided)
- ◎ Salivary fistula managed medically (e.g. anticholinergic medication)
- ◎ Requiring drainage without GA (includes radiologically guided aspiration/drainage)
- ◎ Requiring re-exploration and/or drainage under GA
- ◎ Evidence of single organ dysfunction
- ◎ Evidence of multiorgan dysfunction
- ◎ Patient death

Has the patient experienced an allergic reaction?

- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the allergic reaction

- ◎ Mild reaction not requiring treatment
- ◎ Mild, moderate or severe reaction treated with medication
- ◎ Anaphylactic shock with single organ dysfunction
- ◎ Anaphylactic shock with multiorgan dysfunction
- ◎ Patient death

Has the patient experienced a post-operative chest infection (including aspiration pneumonia)?

- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the chest infection

- ◎ Managed with physiotherapy only
- ◎ Managed with antibiotics
- ◎ Parapneumonic effusion or empyema requiring aspiration or drainage
- ◎ Evidence of respiratory failure (single organ)
- ◎ Evidence of multiorgan dysfunction
- ◎ Patient death

Has the patient experienced a deep vein thrombosis (DVT) or pulmonary embolism (PE)?

- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the DVT or PE

- ◎ DVT or PE managed with anticoagulation only
- ◎ Need for endovascular intervention (including filters) not under GA
- ◎ Need for endovascular intervention or surgical thrombectomy under GA
- ◎ Evidence of PE with respiratory dysfunction
- ◎ Evidence of PE with multiorgan dysfunction
- ◎ Patient death

Has the patient experienced a pneumothorax, haemothorax or both?

- ◎ Yes
- ◎ No

Please tick the option that most accurately represents the severity of the pneumothorax or haemothorax

- ◎ Small pneumothorax or haemothorax managed without a chest drain
- ◎ Pneumothorax or haemothorax requiring a chest drain
- ◎ Haemothorax requiring surgical intervention under GA
- ◎ Evidence of respiratory failure
- ◎ Evidence of multiorgan failure
- ◎ Patient death

Has the patient experienced an acute coronary syndrome (ACS)?

- ◎ Yes
- ◎ N0

Please tick the option that most accurately represents the severity of the ACS

- ◎ Evidence of ischaemia (stable or unstable angina) treated with medication only
- ◎ Myocardial infarction without dysfunction of other organs
- ◎ Myocardial infarction with multiorgan dysfunction

Is there a clinical suspion that the patient may have experienced an air embolism?

- ◎ Yes
- ◎ No

Has the patient experienced any other complications that have not already been mentioned?
◎ Yes
◎ No

Please specify what other complication they have experienced

Please tick the option that most accurately represents the severity of this other complication
◎ Any deviation from normal post-operative course without need for pharmacological, surgical, endoscopic or radiological intervention
◎ Requiring pharmacological treatment with drugs other than those allowed for grade I (see Clavien-Dindo classification below)
◎ Intervention not under GA
◎ Intervention under GA
◎ Single organ dysfunction
◎ Multiorgan dysfunction
◎ Patient Death

APPENDIX A. Classification of Surgical Complications

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)[‡] requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

[‡] brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info

B.10 Drain Output Data Form

DEFeND Drain Output Data Form

Please see flowchart below for explanation

Drain already removed? ◎ No ◎ Yes

Time drain emptied yesterday evening? (dd/mm/yyyy hh:mm) _____

Volume Morning (ml) _____ Time taken (dd/mm/yyyy hh:mm) _____ According to trial protocol the drain should be removed. Has the drain been removed? ◎ Yes ◎ No

Volume Afternoon (ml) _____ Time taken (dd/mm/yyyy hh:mm) _____ According to trial protocol the drain should be removed. Has the drain been removed? ◎ Yes ◎ No

Volume Evening (ml) _____ Time taken (dd/mm/yyyy hh:mm) _____

Drain Rate (Morning) _____

Drain Rate (Afternoon) _____

Actual date and time the drain was removed (dd/mm/yyyy hh:mm) _____

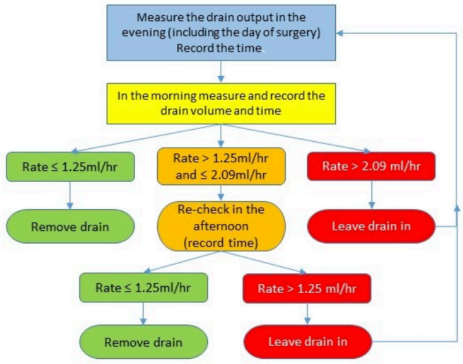
DEFeND Drain Measurement and Removal Protocol

The protocol is based on the widely used cut-off of less than 30ml in 24 hours for drain removal.

Drain output should be measured at a minimum of 2 time points during the day (morning and evening). The contents of the drain are emptied into a measuring cylinder for every reading.

Because these time points may vary slightly from day to day we are interested in the rate of drain output as well as the volume.

The MACRO database will automatically calculate the rate for you. The flow chart describes the decision making process in more detail.



B.11 Hospital Discharge Form

DEFeND Hospital Discharge Form

Is the patient medically fit for discharge?
◎ Yes
◎ No

Who made this decision?

Grade of decision maker
◎ Consultant
◎ Specialty Trainee (or medically qualified equivalent)

Has the patient been discharged from hospital today?
◎ Yes
◎ No

Actual date and time (24 hour clock) the patient left the ward. (dd/mm/yyyy hh:mm)

B.12 End of Trial Form

DEFeND End of Trial Form

Blinding of patient
- ◎ Strongly believe I received fibrin sealant
- ◎ Somewhat believe I received fibrin sealant
- ◎ Somewhat believe I did NOT receive fibrin sealant
- ◎ Strongly believe I did NOT receive fibrin sealant
- ◎ Don't know

Blinding of research nurse
- ◎ Strongly believe the patient received fibrin sealant
- ◎ Somewhat believe the patient received fibrin sealant
- ◎ Somewhat believe the patient did NOT receive fibrin sealant
- ◎ Stroingly believe the patient did NOT receive fibrin sealant
- ◎ Don't know

Blinding of surgeon
- ◎ Strongly believe the patient received fibrin sealant
- ◎ Somewhat believe the patient received fibrin sealant
- ◎ Somewhat believe the patient did NOT receive fibrin sealant
- ◎ Strongly beleive the patient did NOT receive fibrin sealant
- ◎ Don't know

Number of lymph nodes harvested in neck dissection

Please ask the patient the following question:

Fibrin sealant costs approximately £100 per application.

Depending on the results of a future clinical trial we may consider introducing fibrin sealant into routine practice for all patients undergoing the same operation that you had.

In your opinion as a patient and tax payer, what would be the smallest improvement the fibrin sealant would need to offer in a patient's recovery to make it a worthwhile expense?

Minimal clinically important difference (MCID)

B.13 Wound Healing Questionnaire (WHQ Form

DEFeND WHQ

Wound Healing Questionnaire

A. Your wound

Since your surgery...

1. Was ther e redness spreading away from the wound? (erythema/cellulitis)
   - Not at all
   - A little
   - Quite a bit
   - A lot
2. Was the area around the wound warmer than the surrounding skin?
   - Not at all
   - A little
   - Quite a bit
   - A lot
3. Has any part of the wound leaked cleaer fluid? (serous exudate)
   - Not al all
   - A little
   - Quite a bit
   - A lot
4. Has any part of the wound leaked blood-stained fluid? (haemoserous exudate)
   - Not at all
   - A little
   - Quite a bit
   - A lot
5. Has any part of the wound leaked thick yellow/green fluid? (pus/purulent exudate)
   - Not at all
   - A little
   - Quite a bit
   - A lot
6a. Have the edges of any part of the wound separated/gaped open of their own accord? (spontaneous dehiscence)
   - Not at all
   - A little
   - Quite a bit
   - A lot
6b. IF the edges of the wound separated/gaped open, did the deeper tissue also separate?
   - Not at all
   - A little
   - Quite a bit
   - A lot
7. Has the area around the wound become swollen?
   - Not at all
   - A little
   - Quite a bit
   - A lot
8. Has the wound been smelly?
   - Not at all
   - A little
   - Quite a bit
   - A lot
9. Has the wound been painful to touch?
   - Not at all
   - A little
   - Quite a bit
   - A lot
10. Have you had, or felt like you've had, a raised temperature or fever? (fever > 38C)
    - Not at all
    - A little
    - Quite a bit
    - A lot

B. Wound care

Since your surgery...

11. Have you sought advice because of a problem with your wound other than at a planned follow-up appointment?
    - Yes
    - No
12. Has anything been put on the skin to cover the wound? (dressing)
    - Yes
    - No
13. Have you been back into hospital for treatment of a problem with your wound?
    - Yes
    - No
14. Have you been given antibiotics for a problem with your wound?
    - Yes
    - No
15. Have the edges of your wound been deliberately separated by a doctor or nurse?
    - Yes
    - No
16. Has your wound been scraped or cut to remove any unwanted tissue? (debridement of wound)
    - Yes
    - No
17. Has your wound been drained? (drainage of pus/abscess)
    - Yes
    - No
18. Have you had an operation under general anaesthetic for treatment of a problem with your wound?
    - Yes
    - No

Total ☐

B.14 Wound Healing Questionnaire (WHQ) Validation Form

DEFeND WHQ Validation

Wound Healing Questionnaire (WHQ) Validation Questions for Clinician

Date of assessment

Time of assessment

Hospital

Abscess or other evidence of infection found during re-operation, by radiological or histopathological examination	◎ Yes ◎ No
Aspirated fluid/swab of surgical site yields organisms and pus cells present	◎ Yes ◎ No
Clinicians diagnosis	◎ Yes ◎ No
Fever (temperature 38C or more)	◎ Yes ◎ No
Heat	◎ Yes ◎ No
Incision spontaneously dehisces or opened by surgeon	◎ Yes ◎ No
Localised pain and tenderness	◎ Yes ◎ No
Localised swelling	◎ Yes ◎ No
Purulent drainage	◎ Yes ◎ No
Redness	◎ Yes ◎ No

Type of SSI

◎ None
◎ Superficial
◎ Deep
◎ Organ/space

B.15 Electronic Case Report Form Completion Guidelines

DEFeND

eCRF Completion Guidelines

Title of Research Project: DEFeND
EudraCT Ref (if applicable):
Chief Investigator: Andrew Schache
Sponsor(s): University of Liverpool
Sponsor(s) Reference Number(s): UoL001346
Funder name and ref (if applicable): NIHR DRF-2017-10-117

The DEFeND Trial will capture data using electronic Case Report Forms (eCRF) which will be completed by delegated members of the research team at site using the MACRO database.

MACRO user guide (INS_D008) is available via the LCTU portal.

Data Capture Method at Site

With the exception of SAE forms, all data should be entered onto the MACRO trial database by a delegated member of the research team, ensuring all entries are accurate and verifiable with the source data in the medical record. Any discrepancies with source data should be explained by adding a note to the MACRO database.

Patient Questionnaires

Patient questionnaires include:

- Neck Dissection Impairment Index (NDII)
- Pain Visual Analogue Scale (VAS)
- Bluebelle Wound Healing Questionnaire (WHQ)

Baseline NDII and Pain VAS should be completed pre-operatively. The Pain VAS is then completed every inpatient day post-operatively and every scheduled clinical follow-up until the patient exits the trial. The NDII and Buebelle WHQ are completed at the last clinic encounter before the patient exits the trial (i.e. 4-6 week clinic appointment or premature exit from the trial). The completed questionnaires should be stored within the medical notes and transcribed into the MACRO database at the earliest opportunity.

SAE Forms

SAE forms should **not** be entered into MACRO. They should be completed on paper, signed by an investigator and emailed to defend@liverpool.ac.uk.

Data Queries

The DEFeND trial team will perform a cross check and verification of MACRO discrepancies for data entered and will raise queries when appropriate, including missing data.

All data should be entered onto the MACRO system in real time or as soon as feasibly possible. Sites should resolve and address data queries within 7 days. If an answer to a data query cannot be provided please answer 'NK' (Not Known) or 'N/A' (Not Applicable). The data manager will close the query once resolved. Please refer to **SSDEF_D016 – Data Query Process for DEFeND Trial** for further details.

Signing Forms

- The eligibility criteria must be electronically signed-off by the PI on the MACRO system before any further data can be entered.
- The consent form is electronically uploaded onto the LCTU portal for 2 independent validity checks to be undertaken by the DEFeND trial team. The trial team will individually check the consent forms and sign-off on their validity before permanently deleting the electronic version. The original signed document will remain in the patient's medical records. LCTU will not store any copies of source data documents.
- The 'Pre-Randomisation Checklist' is signed-off by a delegated member of the research team at site before randomisation can take place.
- SAE forms require signatures from the principal investigator or Co-Investigator (as named on the delegation log).
- The PI has overall responsibility for the accuracy of data reported on the eCRF.

Eligibility & Randomisation

- For detailed randomisation instructions please refer to the DEFeND randomisation instructions which are available via the LCTU portal www.lctu.org.uk.
- Screening numbers are generated by logging on to the LCTU portal at www.lctu.org.uk and entering details into the screening log. Sites should log all individuals screened, even if patients decline the invitation to participate or if they are screening failures.
- The eligibility criteria should be completed on MACRO by a delegated member of the research team and electronically signed-off by the PI.
- If the patient is ineligible or declines, please indicate why on the screening log on the LCTU portal.
- Randomisation is performed by sites via the TARDIS software. The allocation will not be revealed within MACRO, only the patient's consultant (or delegated other0 will receive an email with a link to the allocation reveal. The allocation is to be revealed at the point of wound closure intra-operatively. A patient cannot be randomised until their 'Pre-Randomisation Checklist' has been completed on MACRO.

Serious Adverse Events (SAE)

- Please refer to **SSDEF_D009 – DEFeND Safety Plan** for further details.
- Only report the following SAEs to the LCTU:
    - Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien Dindo **grade IV or above**.
    - An exacerbation of a pre-existing illness/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant **grade IV or above**.
    - An increase in frequency or intensity of a pre-existing episodic event/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant **grade IV or above**.
    - A condition (even though it may have been present prior to the start of the trial) detected after the trial surgery and/or use of ARTISS fibrin sealant **grade IV or above**.
    - Continuous persistent disease or symptoms present at baseline that worsens following the trial surgery and/or use of ARTISS fibrin sealant **grade IV or above**.
- All other SAEs should be recorded in patients' medical notes in accordance with local NHS policy.
- SAEs should be reported to the LCTU within 24 hours of site becoming aware of it.
- All follow up SAE data must be reported to the LCTU within 24 hours of site becoming aware of it.
- Please download hard copies of the SAE CRF from the LCTU portal (www.lctu.org.uk) and complete and email it to defend@liverpool.ac.uk.
- SAE forms should be completed/signed off by a medically qualified and delegated clinician (as indicated on the delegation log).
- If you are unable to download the SAE CRF, please contact the DEFeND Trial Team via email on defend@liverpool.ac.uk or contact the TC (Mandeep Bajwa) on 07950583792.
- File in the Investigator Site File.
- The DEFeND Trial Team will e-mail an acknowledgement to research sites to confirm receipt of the SAE. If an acknowledgment is not received please contact the LCTU Trial Co-ordinator directly (Mandeep Bajwa, Tel: 07950583792).
- The minimum dataset required for a preliminary report should include the following. These are included as fields on the SAE forms
    - Patient trial number and initials

- Date of onset of event
- Brief description of event
- The reason why the event is classified as serious
- Causality relationship – investigator's assessment of the association between the event and either the study treatment or the surgical procedure.

- Please complete SAEs with as much information as is available to you at the time of reporting.

eCRF Forms

The eCRF is composed of the following forms:

- Screening Form
- Eligibility form
- Baseline Form
- Neck Dissection Impairment Index (NDII)
- Neck Pain Scale
- Randomisation Form
- Surgery Form
- Post-Operative Complication Form
- Drain Output Data Form
- Hospital Discharge Form
- Wound Healing Questionnaire (WHQ)
- Wound Healing Questionnaire Validation (WHQV) Form
- End of Trial Form

Prior to randomisation the Screening, Eligibility, Baseline, NDII, Neck Pain Scale and randomisation forms need to be completed. On the day of surgery the Surgery Form should be completed in theatre **prior to the allocation being revealed.** The follow-up schedule is divided into Inpatient Daily Assessments, Follow-up 1 (day 7-14) and Follow-up 2 (day 28-42). For Inpatient Daily Assessment the Post-Operative Complication, Neck Pain Scale, Drain Output Data and Hospital Discharge forms need to be completed every day of the patients hospital stay. For Follow-up 1 (and any unscheduled visits) the Post-Operative Complication and Neck Pain Scale forms should be completed. For Follow-up 2 the NDII, Neck Pain Scale, WHQ, WHQV, Post-Operative Complication and End of Trial forms should be completed.

eCRF Completion Guide

Screening Form - all questions are mandatory

1. Patient Initials. There is room for up to 3 letters.
2. NHS Number. There is room for up to 10 numbers. There is no allowance for spaces, punctuation or dashes.
3. Date of birth. Please type in the date of birth using the dd/mm/yyyy format and include the 'forward slash' punctuation in your entry.
4. Gender. Male or female, tick the most appropriate.
5. Screening Number. There is room for up to 15 alphanumeric values.
6. Hospital Site. Tick either Aintree University Hospital or Queen Victoria Hospital depending on where the patient is being treated.
7. Consultant. Please select the consultant from the drop down list.
8. Has a Patient Information Sheet (PIS) been provided? Tick either yes or no. Please provide the version number of the PIS handed to the patient. There is space for a number with 1 decimal place e.g. 2.1. If the version number is a whole number e.g. 2, please type 2.0. Please type in the date that the PIS was handed to the patient using the dd/mm/yyyy format and include the 'forward slash' punctuation in your entry. Please note that a patient cannot be randomised unless this question is ticked yes and version and dates have been completed in full.
9. Trial consent form signed? Tick either yes or no. Please provide the version number of the consent form used to consent the patient. There is space for a number with 1 decimal place e.g. 2.1. If the version number is a whole number e.g. 2, please type 2.0. Please type in the date that the patient consented to participating in the trial using the dd/mm/yyyy format and include the 'forward slash' punctuation in your entry. Please note that a patient cannot be randomised unless this question is ticked yes and version and dates have been completed in full.

   Once the yes button has been ticked an automated email will be sent to the DEFeND trials team to centrally check the consent form. Two independent members of the trial team will perform the checks and electronically authorise the consent on MACRO. Once both electronic signatures have been entered the consent will be validated.

   The signed consent form must be scanned and uploaded to the LCTU portal following the steps below: Login to LCTU portal using your username and password.

   a. Click on the 'Portal Home' button in the top right hand corner.
   b. Click on the 'DEFeND' box.
   c. Select the hospital where the patient is being treated.

d. You should now be on a page with several green boxes on the left hand side of the screen. Please select the 'Transfer Files' box.

e. This will take you to the 'Trial Secure File Transfer' page. Please click on the 'Upload File' box in the top right hand corner of the screen.

f. Upload the scanned version of the consent ensuring all pages are included. **The name of the file should be the screening number of the patient**. Please do not use the patient's name or initials.

Eligibility Form - all questions are mandatory

1. Inclusion and Exclusion Criteria. Work through the criteria sequentially ticking either yes or no. If the patient does not meet the criteria the form will freeze and no further questions can be answered. The patient cannot be randomised.

2. Once the eligibility criteria have been met the researcher can tick the 'patient has met the eligibility criteria' button. This will open a box for the researcher to enter their user name and password and electronically sign-off there entry. Once this has been done an automated email will be generated to the PI informing them that the eligibility criteria need to be signed-off by them.

3. PI's electronic signature. The PI will need to login to MACRO and enter the Eligibility Form. If they are content that the patient has met the eligibility criteria they may tick the 'PI click here to sign' box. This will open a box for the PI to enter their username and password and electronically sign-off the eligibility criteria. Once this has been done the 'Eligibility criteria signed off by PI?' question in the Randomisation Form will be automatically populated with a 'Yes' response.

Baseline Form

1. Site of primary tumour (mandatory). Please select the most appropriate site from a drop-down menu. If the patient has a neck recurrence following previous treatment, please document the site of the original primary tumour. If the site is not listed please specify in the subsequent box providing as much information as possible (maximum 100 characters).

2. Histology (mandatory). Please type the histological diagnosis (e.g. squamous cell carcinoma or SCC). If the histological diagnosis is uncertain prior to surgery please document this in the text box with any supporting information (maximum 100 characters).

3. Has the patient had previous treatment/interventions to the neck? (mandatory). Please select the most appropriate option from the list. If the patient has had contralateral neck surgery **without** radiotherapy this should be recorded as 'no previous treatment/intervention'. If the patient has had contralateral neck surgery **with** radiotherapy record this as 'previous ipsilateral radiotherapy' or 'previous contralateral radiotherapy' depending on laterality. If the patient has had previous bilateral radiotherapy record this as 'previous ipsilateral radiotherapy'. If the options from the list are not representative of the patient's previous treatment please select 'other' and provide details in the subsequent box (maximum 100 characters).

4. Height (mandatory). Please enter the patient's height in meters to 2 decimal places i.e. to the nearest centimetre. 165 cm should be recorded as 1.65 m and 180 cm should be recorded as 1.80 m. Any height up to 9.99 m is recordable.

5. Weight (mandatory). Please enter the patient's weight in kilograms to 1 decimal place (75 kg should be recorded as 75.0 kg). Any weight up to 999.9 kg is recordable.

6. BMI. Automatically calculated based on height and weight.

7. WHO Performance Status (mandatory). Please select from the drop down list.

8. Smoking (mandatory). Pease select the most appropriate option from the list. If the patient is a current smoker or has previously smoked please document how many years (whole number up to 99) they have smoked for and the average number of cigarettes (or equivalent) they smoked per day during this time (whole number up to 999). Pack years is automatically calculated.

9. Average number of alcohol units consumed per week (mandatory). Please select the most appropriate option. If the patient drinks more than 14 units please indicate whether there is a history (or clinical suspicion) of alcohol abuse or dependence by selecting yes or no.

10. Diabetes (mandatory). Please indicate if the patient has an established diagnosis of Diabetes (type 1 or type 2) by ticking yes or no.

11. Is the patient on immunosuppressant medication? (mandatory). Please indicate if any of the existing medications that the patient takes have immunosuppressant properties by ticking yes or no.

12. Bleeding disorder (mandatory). Please indicate if the patient has a formally diagnosed bleeding disorder (i.e. a disease that results in altered coagulation and tendency to bleed excessively) by ticking yes or no.

13. Is the patient on regular antiplatelet medication? (mandatory). Please indicate whether the patient takes regular antiplatelet medication, even if it is planned to be stopped pre-operatively, by ticking yes or no.

14. Is the patient on more than one antiplatelet? (mandatory). Please indicate if the patient takes more than one antiplatelet, even if one or more are planned to be stopped preoperatively, by ticking yes or no.

15. Is the patient on regular anticoagulant medication? (mandatory). Please indicate whether the patient takes regular anticoagulant medication, even if it is planned to be stopped pre-operatively, by ticking yes or no.

16. Pre-operative blood results (required but not mandatory). Please provide the results of the most up-to-date pre-operative blood results. Units and reference ranges are provided so please ensure the result is correctly entered. It is expected that the blood results are entered if they are available. However, if they are not clinically indicated, the trial protocol does **not** insist on them being done for research purposes alone.

Questionnaires

Please download and print the questionnaire along with the questionnaire cover sheet from the CRF Form Library on the LCTU portal. Complete the cover sheet providing the following details:

1. Patient screening number
2. Patient initials
3. Date of completing the questionnaire
4. Name of questionnaire
5. Visit in which questionnaire completed

Once the patient has completed the questionnaire please transcribe their responses into MACRO

Neck Dissection Impairment Index (NDII)

Please print out the NDII from CRF Form Library in the LCTU portal and hand to the patient to complete. Once the patient has completed the questionnaire please transcribe the responses onto MACRO. Both the raw NDII score and standardised NDII score are automatically calculated. Please refer to the 'Transposing Questionnaires to MACRO' guidance below.

Neck Pain Scale

Please print out the Neck Pain Scale from the CRF Form Library in the LCTU portal and hand to the patient to complete. Please record the numerical value (with up to 1 decimal place of accuracy) that most corresponds with the patient's mark. This may be done with the help of a ruler. Please refer to the 'Transposing Questionnaires to MACRO' guidance below.

Wound Healing Questionnaire (WHQ)

Please hand a hard copy of the WHQ from the CRF Form Library and hand to the patient to complete. Once completed please transcribe the responses into MACRO. The score will be automatically calculated. Please refer to the 'Transposing Questionnaires to MACRO' guidance below.

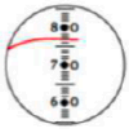
Wound Healing Questionnaire Validation Checklist (WHQV)

This is to be completed by a blinded clinician during follow-up 2. If the clinician has a MACRO username and password they may complete the form directly. If not, the research nurse may need to hand the clinician a hard copy of the WHQV and transcribe the responses themselves. Please refer to the 'Transposing Questionnaires to MACRO' guidance below.

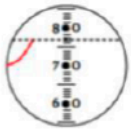
Transposing Questionnaires to MACRO

The following examples are a guide to how patient responses on the different questionnaires should be transposed to MACRO. Please remember if there is uncertainty the patient should be asked for clarification before recording a result as 'unobtainable'.

1. When a patient marks the Neck Pain Scale incorrectly, with either a curved line, or next to the scale:



For example this response should be coded as 77



Even though the line does not cross the VAS this response can still be scored by drawing a horizontal line from the end point of the response to the VAS. In this example the response should be coded as 77

figure 1

2. When the patient circles the VAS:

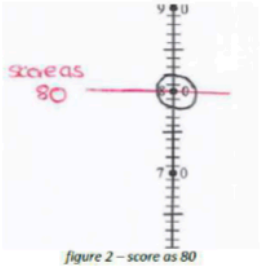


figure 2 – score as 80

Figure 2 shows an example of the subject circling the point on the vertical axis where he feels his health state is. There are thus two lines crossing the vertical axis and per the EQ VAS user guide this should be recorded as missing data. However, the intention of the subject seems clear, and in such instances the health state should be recorded as half-way between the two points at which the circle crosses the vertical axis. In our example this is a score of 80.

3. When a patient marks next to, rather than on, the VAS:

figure 3 – score 70

Figure 3 shows a vertical line parallel to the 0-100 scale. Although the line does not originate at the box marked "your own health state today", and does not cross the vertical scale, the intention of the subject is clear. In such instances the result can still be entered onto the database by drawing a horizontal line from the top of the subject's line to the vertical scale. In this example the score is 70.

4. When a patient uses several markings in place of a single line:

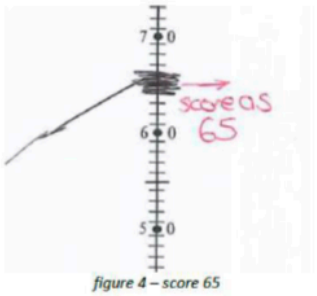


figure 4 – score 65

Figure 4 shows a thick horizontal line scored through the vertical scale across several markings. In such cases the score should be taken from half-way between the top and the bottom of the scored line, in this case a score of 65.

Follow the instructions in the figures below when transposing data from either the NDII or WHQ questionnaires

5. When a patient has crossed through one answer but has clearly circled another:

figure 5 – code as 3

6. When a patient has circled two answers:

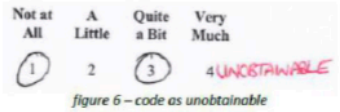


figure 6 – code as unobtainable

7. When a patient indicates their answer may lie between two points:

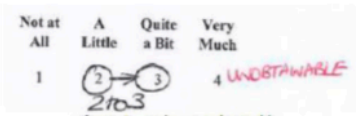


figure 7 – code as unobtainable

Randomisation Form

The pre-randomisation checklist includes:

- Consent form version and date (CRF entry automatically populated)
- Central authorisation signatures of valid consent (completed by DEFeND Trial Team)
- Eligibility criteria signed by PI (CRF entry automatically populated)
- Baseline NDII and Neck Pain Scale (CRF entry automatically populated)
- Electronic signature from research site to confirm all the above have been completed

Once the 'please click here to sign-off pre-randomisation checklist' button has been clicked and the researcher has electronically signed the authorisation, the patient can be randomised. Ideally this should be done before the day of surgery to avoid any technical problems that may prevent the patient from being randomised. Randomisation is performed in a separate programme called TARDIS. Please refer to document **SSDEF_D011 - DEFeND Randomisation Instructions** for details

on how to randomise the patient. Once the patient is randomised the 'patient has been randomised successfully' button will be automatically ticked. The consultant assigned to the patient will receive an automated email informing them that the patient has been randomised and a link to the allocation reveal.

Surgery Form - all questions are mandatory

1. Date of Surgery. Please type in the date of surgery using the dd/mm/yyyy format and include the 'forward slash' punctuation in your entry.

2. ASA (American Society of Anaesthesiologists physical status classification). Please select the most appropriate grade from the list. Please take this information from the anaesthetist or anaesthetic records.

3. Start time of surgery. Please record the start time of the surgery i.e. when the surgeon makes their first incision using the 24 hour clock and colon punctuation (hh:mm).

4. Is the patient undergoing a concurrent mucosal resection? Please indicate whether the patient is undergoing a mucosal resection of the pharynx, larynx or oral cavity (e.g. of the primary tumour) during the same operation as the neck dissection by ticking yes or no. Please note that if the patient is undergoing concurrent resection of skin, salivary gland, thyroid, orbit or paranasal sinuses without pharyngeal, laryngeal or oral mucosal involvement please tick no.

5. Neck levels dissected. Please tick all the neck levels that were dissected during the neck dissection between levels I-VI. Please note a minimum of three levels need to be dissected to meet eligibility criteria. The 'Number of neck levels dissected' box will be automatically populated.

6. What cutting instrument was used to carry out the majority of the dissection? Please tick the most appropriate option. It is expected that many surgeons will use a combination of these instruments at various points during the surgery. Please tick the instrument that was used to perform >50% of the dissection. If the surgeon has used another instrument not listed to perform >50% of the dissection please specify the instrument in the subsequent box (max 100 characters).

7. Estimated blood loss. Please record the estimated blood loss in millilitres. This is normally estimated using a combination of blood stained swabs and volume of fluid in the suction container. Any volume up to 9999ml is recordable.

8. Time when ready for wound closure. Please record the time when the neck dissection wound was ready for closure using the 24 hour clock and colon punctuation (hh:mm).

9. Surgeons present in theatre. Please list all the surgeons present in theatre when the wound was ready for closure using the drop down lists provided. Any non-essential members of the surgical team should leave theatre at this point. It is permissible for any surgeon to be present during surgery as long they leave theatre prior to wound closure if their presence is not essential. If a surgeon leaves before the point of wound closure they are not required to be listed in the form. If a surgeon's name is not listed in the form they should not be

present when the allocation is revealed. Any surgeon listed as being present will not be permitted to carry out any post-operative assessment. There is no restriction on anaesthetic and theatre staff.

10. Once points 8 and 9 above have been completed the lead surgeon in theatre can use the link in the automated email sent after randomisation to access the allocation. The lead surgeon may delegate this responsibility to another individual who has their own login for TARDIS. The surgeon will be asked to login to access the allocation and their name, date and time of accessing the allocation will be recorded.

11. Allocation revealed. This button will be automatically ticked to yes once the allocation has been accessed.

12. Time patient left recovery. Please record the time the patient left theatre recovery to go to the ward using the 24 hour clock and colon punctuation (hh:mm).

Please note that if the allocation is revealed at a date or time outside of the limits of 'Time when ready for wound closure' and 'Time patient left recovery' an automatic protocol deviation will be recorded.

Assessment of Post-Operative Complications Form - all questions are mandatory

Please note that this form is completed for each day that the patient is in hospital and any subsequent follow-up visits (scheduled or unscheduled) prior to exiting the trial

1. Has the patient experienced any complications as a result of their recent surgery? Please indicate whether the patient has experienced a complication by ticking yes or no.

2. Please record name of the clinician making assessment for complications. Please select the name of the clinician making the assessment of complications from the drop down list. Please note that if the clinician is not listed they should not be performing trial related assessments. If the clinician is listed as being in theatre for this patient, an automatic protocol deviation will be recorded.

3. Please record the grade of clinician making assessment for complications. Please tick either consultant or specialty trainee. Please note that the clinician needs to be medically qualified and of appropriate clinical seniority to make this assessment.

4. The following common or expected complications have been listed.

    a. Neck wound infection

    b. Other surgical site infection

    c. Haematoma or bleeding

    d. Neck wound breakdown or fistula

    e. Chyle leak

    f. Seroma or sialocele

g. Allergic reaction

h. Chest infection including aspiration pneumonia

i. Deep vein thrombosis or pulmonary embolism

j. Pneumothorax, haemothorax or both (haemopneumothorax)

k. Acute coronary syndrome

l. Air embolism

For each of these complications please tick 'yes' only once they have been diagnosed by the clinician making the diagnosis. In cases where diagnostic tests are required to make a diagnosis please only tick 'yes' once these test have been performed and the presence of the complication confirmed. Once a complication has been diagnosed please grade the severity using the options provided. You are required to tick 'no' if the complication is not present - please do not leave the 'yes' 'no' option blank. If the patient experiences a complication not listed please specify the complication in box provided towards the bottom of the form (max 100 characters). If this selection is made you are required to grade the severity using the Clavien-Dindo classification which is provided at the bottom of the form. If there is uncertainty on how the complication should be graded please refer to **Appendix A** of the protocol (**SSDEF_PROTOCOL**). If uncertainty remains please contact the DEFeND Trial Team for further advice (defend@liverpool.ac.uk).

Drain Output Data Form - all questions are mandatory

Please note that the management of the drain has been protocoled. Decision to remove, re-measure or keep the drain are made based on the volumes and times entered on this form. Blinded clinicians who are making outcome assessments may overrule the protocol for safety reasons. A flow chart has been provided below and in the eform for reference. Drain output measurements using measuring cylinders need to be undertaken twice daily.

1. Time drain emptied yesterday evening? Please record the date and time using the dd/mm/yyyy hh:mm format. Please note that punctuation (: & /) as well as a single space between date and time are essential for correct entries.

2. Volume Morning and Time taken. Please record the volume of fluid in the drain in millilitres (ml) in the morning and record the date and time the measurement was taken using the dd/mm/yyyy hh:mm format.

   i) If the rate of drain output is low enough for drain removal the question 'According to the trial protocol the drain should be removed. Has the drain been removed?' will light up. Please tick either 'yes' or 'no'.

   ii) If you tick 'yes' the 'Actual date and time the drain was removed' question will light up. Please enter the date and time using the dd/mm/yyyy hh:mm format.

3. If the rate of drain output is intermediate the 'Volume Afternoon' question will light up. Under these circumstances the protocol requests that the drain output be re-measured in

the afternoon. Ideally this should be around lunchtime so that the patient can still be discharged if the drain is removed at this time. Please record the volume of fluid in the drain in millilitres (ml) in the afternoon and record the date and time the measurement was taken using the dd/mm/yyyy hh:mm format. Follow points 2(i) and 2(ii) if the rate of drain output is low enough for removal.

4. If the rate of drain output is high the 'Volume Evening' question will light up. Under these circumstances the protocol requests that the drain be left in the patient. Please record the volume of fluid in millilitres (ml) in the evening and record the date and time using the dd/mm/yyyy hh:mm format. Because this reading is taken outside of the normal working hours of the research team, it does need to be transcribed onto MACRO in real time. Ward nurses should record the volume, date and time in the patient's drain or fluid balance chart for the research team to transcribe into MACRO the following morning. Arrangements for weekend cover will need to be made locally.

If the MACRO system is down and drain volumes and times cannot be entered or the researcher making assessments does not have access to MACRO the rate of drain output will need to be calculated manually by dividing the number of millilitres of fluid in the drain by the number of hours since the drain was last emptied. Please see the flow chart below for further guidance on the protocol.

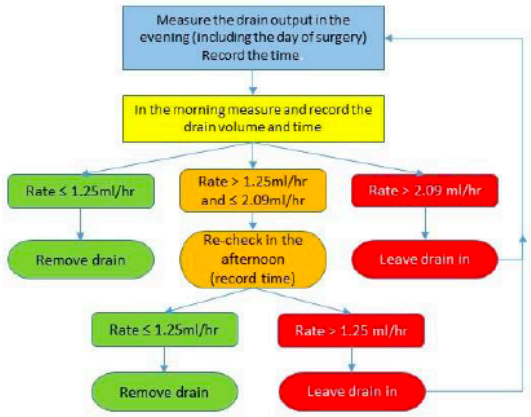
DEFeND Drain Measurement and Removal Protocol

The protocol is based on the widely used cut-off of less than 30ml in 24 hours for drain removal.

Drain output should be measured at a minimum of 2 time points during the day (morning and evening). The contents of the drain are emptied into a measuring cylinder for every reading.

Because these time points may vary slightly from day to day we are interested in the rate of drain output as well as the volume.

The MACRO database will automatically calculate the rate for you. The flow chart describes the decision making process in more detail.



Hospital Discharge Form

1. Is the patient medically fit for discharge? Please indicate whether the patient is medically fit for discharge using 'yes' or 'no' buttons. It is expected that the drain will have been removed prior to this question being answered 'yes'.
2. Who made this decision? Please select from a drop down list.
3. Has the patient been discharged from hospital today? Please indicate whether the patient has been discharged using the 'yes' or 'no' buttons. If 'yes' is selected the subsequent question, 'Actual date and time the patient left ward', will light up. If lit up please enter the date and time using the dd/mm/yyyy hh:mm format.

End of Trial Form

1. Blinding of patient. Please ask the patient whether they think they received the fibrin sealant selecting the most appropriate response from the list provided.

2. Blinding of Research Nurse. Please ask the Research Nurse whether they think the patient received the fibrin sealant selecting the most appropriate response from the list provided.

3. Blinding of Surgeon. Please ask the blinded surgeon assessing outcomes in the last clinic appointment whether they think the patient received the fibrin sealant selecting the most appropriate response from the list provided.

4. Number of lymph nodes harvested in neck dissection. Please transcribe the number reported in the final histology report into this box.

5. Minimal clinically important difference. Please ask the patient:

   "Fibrin sealant costs approximately £100 per application. Depending on the results of a future clinical trial we may consider introducing fibrin sealant into routine practice for all patients undergoing the same operation that you had. In your opinion as a patient and tax payer, what would be the smallest improvement the fibrin sealant would need to offer in a patient's recovery to make it a worthwhile expense?"

   This will be a difficult concept for some patients to grasp. The question contains a free text box (max 1000 characters) please transcribe the patient's response, whatever it may be, into the box. It is deliberately vague to allow the patient to answer freely and based on their own priorities in recovery after surgery. If the patient does not wish to answer the question it can be left unanswered.

B.16 Data Query Process

eCRF Data Query Process for DEFeND Trial

Version 1.0
07/09/2018

ISRCTN Number 99181100

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1. Introduction

This Data Query Process Plan is in place to help guide the conduct of the DEFeND trial. This plan details the Data Query process for DEFeND, and aims to ensure that the data queries are generated and resolved as far as is possible

Specifically the plan will identify:

- The Data Query Processes
- Who is responsible for the processes
- How the processes are performed.
- Who will perform them

2. Trial Background

Please see DEFeND – Data Management Plan (SSDEF_D008) for details of the trial background

3. Data Queries

Data queries or DQs - also referred to as discrepancies or DCRs - are generated when data from electronic Case Report Forms (eCRFs) are completed on the trial database, MACRO. Queries arise if data are missing, appear invalid or fall outside pre-specified ranges. Data queries raised in MACRO may be automated and pre-specified (when validation rules are contravened) or manual, upon review by a member of the DEFeND team.

Data queries will be the responsibility of the trial management team at the Liverpool Clinical Trials Unit (LCTU) who will create, distribute and enter resolved queries on the MACRO database. The DEFeND trial team will communicate with site staff to ensure that queries are resolved at site via the MACRO database.

This plan is used alongside the rules for entering CRF data incoming to the LCTU, included in Section 6.2 in the study specific Data Management Plan (DMP). Data queries are resolved according to the timelines set out in the section 3.4 of this document.

3.1 Raising Data Queries

Data queries are raised when data are missing, appear invalid or fall outside the pre-specified range:

- Data are entered onto the MACRO database (eCRF) by the research staff at site using eCRFs.

- If data entered is not within acceptable validation range, MACRO will highlight the potential for raising a data query for out of range data by displaying a yellow triangle. Alternatively, the DEFeND trial team can manually raise a query for

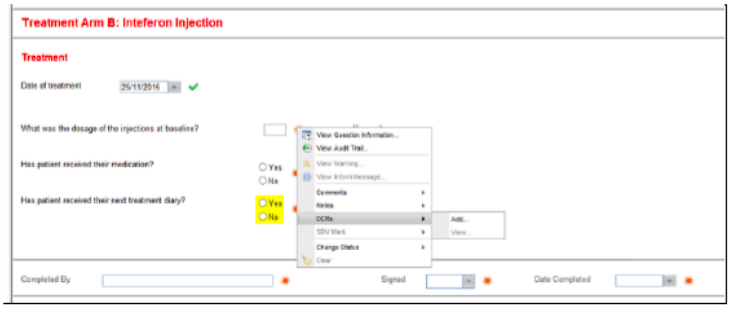
data that is within acceptable ranges but is not acceptable for any of the reasons listed in section 6.2 of the trial Data Management Plan (e.g. illegible, ambiguous, has been incorrectly crossed).

- The DEFeND trial team will right click the question's status icon and raise a 'DCR' (data query).

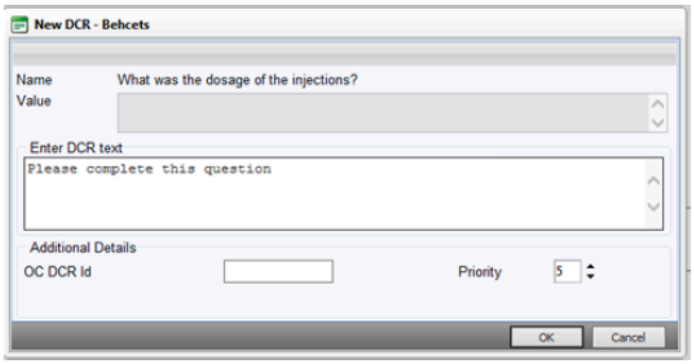
  Once the new data query field box is open the DEFeND trial team will enter the most appropriate text to describe the data query. This is to ensure MACRO tracks the data query with all the necessary information.

The following process is employed to ensure that data queries are generated when using an eCRF system;

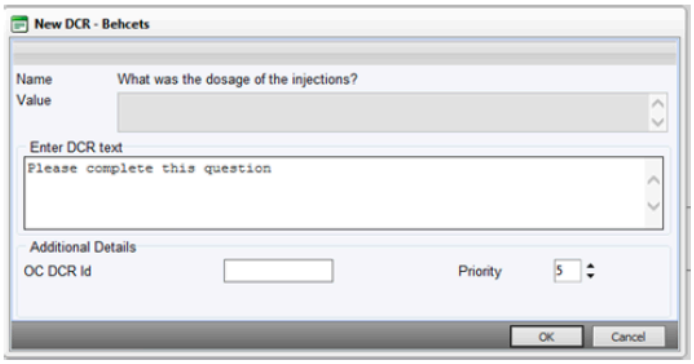
- Data are entered onto MACRO remotely at site by the research team.
- The DEFeND trial team at LCTU will check all data that have been entered.
- If data is deemed inconsistent, inaccurate or missing by the DEFeND trial team at LCTU, a data query is raised if data is on MACRO with as much detail as possible to aid the site in answering the query.
- The DEFeND trial team will right click the questions' status icon and raise a data query.



- Once the new 'DCR' (data query) field box is open enter the most appropriate text to describe the data query. This is to ensure MACRO tracks the data query with all the necessary information.



- Note the red flag to indicate a raised 'DCR' (data query) on this question:

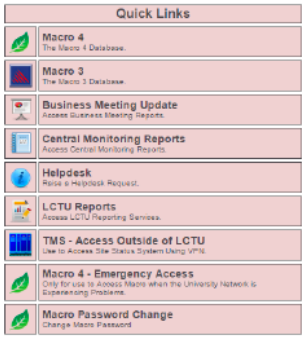


An explanation must be provided when the data query is raised. As much information as possible should be entered at this stage as this will allow the Data Clarification Form (DCF) to be understood clearly by site staff.

Data queries can also be asked via email. If this is done, a data query ('DCR') must still be generated but the text should just state "data query sent via email on <<enter date of email>>".This email and any data query response sent via email must be printed and filed with the relevant CRF pages within the patient's folder.

3.2 Generating Data Clarification Forms (DCFs)

Data Clarification Forms (DCFs) contain a report of outstanding trial data queries and they are generated automatically from data entered into the MACRO database. The DCF report can be accessed through 'LCTU Reports' under Portal Administration on the LCTU portal. The reports are generated in real time and can be printed or saved in a variety of formats. *Please note that 'LCTU Reports' only works in Internet Explorer and not in other internet browsers.*



The DCF can be automated if requested. Each site will receive a pdf attachment of the DCF for each of their patients, listing the outstanding queries against each question.

DCF's can be filtered by individual patient, visit, form, study site or any combination of these.

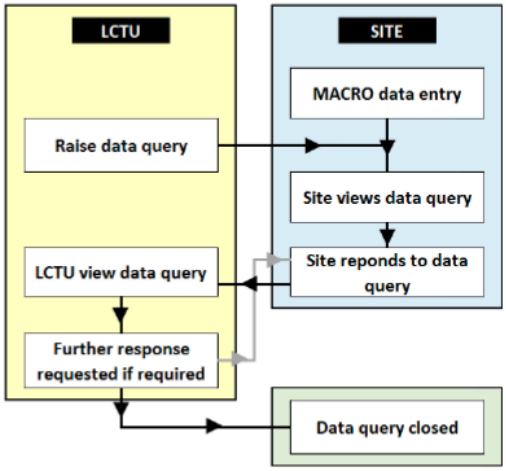
3.3 Distribution of Data Clarification Forms (see APPENDIX 1)

The DCF report allows data queries to be either printed and faxed to site or exported as a pdf. These can be emailed manually or automatically on a specific date and time. The database allows filtering of data queries by patient number, visit, CRF, trial site or any combination of these. Upon selecting filter options, the 'View Report' button is pressed and the report is generated accordingly. This document can then be saved as appropriate and used as an attachment to an email.

For record keeping purposes, DCF's should always be saved as a PDF.

Data queries should be saved in the Research Site subfolders of the Trial Master file.

Data Query Process



3.4 How Sites Respond to Data Queries

Upon receipt of the data clarification forms (See DCFs), it is the responsibility of the research staff at site to respond to the queries manually by entering the answer on the printed DCF. The Trial specific data completion guidelines should be referred to when completing data queries, to clarify the process of responding to the data queries.

Once the data queries are raised in MACRO, the DEFeND trial team should inform sites that there are data queries that need to be responded to.

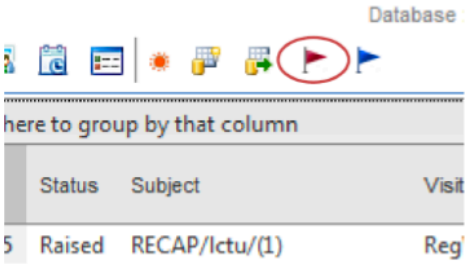
Research site staff can log on to MACRO and list all the data queries ('DCRs) raised for the study by clicking on the red flag icon or all missing data fields by clicking the orange sun icon.

3.5 Resolving Data Queries

At site
Data queries should be resolved within 14 days of receipt by site staff wherever possible. Data queries can be resolved on MACRO or by completing the DCF report sent to site.

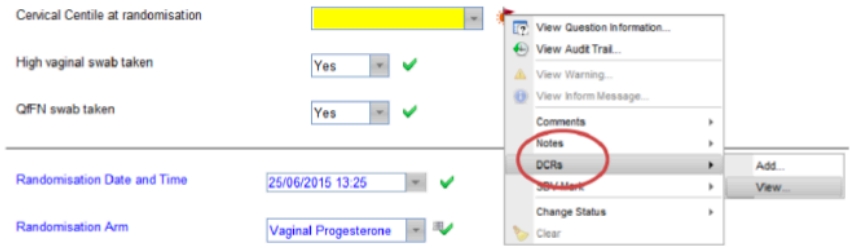
On MACRO

- Site logs on to MACRO and click the red flag icon to display a list of all 'DCRs' (data queries).

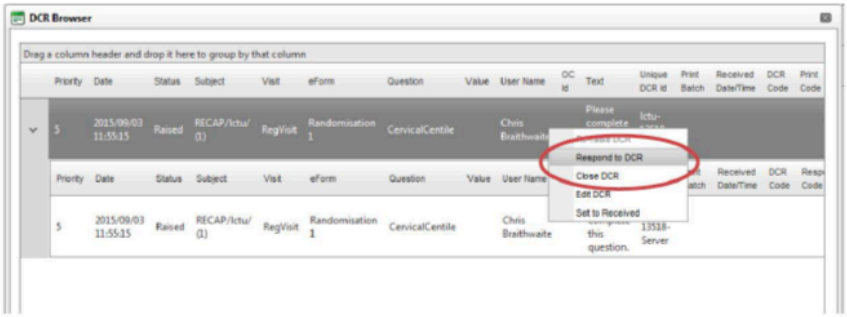


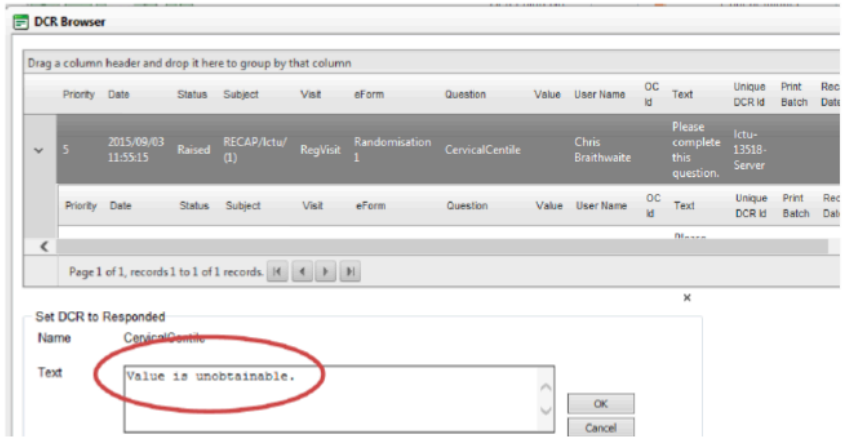
- A list of all 'DCRs' (data queries) will be displayed.

- By double clicking on the DCR in the list, site will be taken to the eForm the DCR is on. From here, site views the DCR by right clicking and selecting 'DCR' and 'view' from the menu.

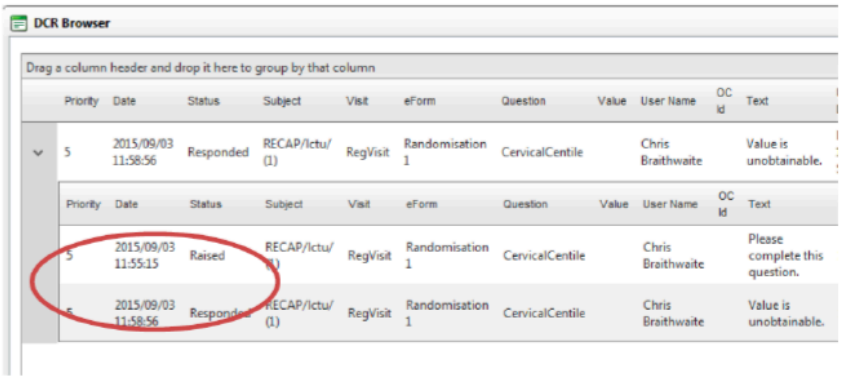


- From here site can respond to the DCR by right clicking on it and selecting 'Respond to DCR'.





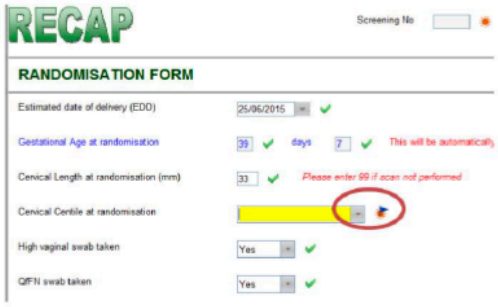
- The audit trail for the DCR will now state 'Raised' and 'Responded'.



Priority	Date	Status	Subject	Visit	eForm	Question	Value	User Name	OC Id	Text
5	2015/09/03 11:58:56	Responded	RECAP/Ictu/ (1)	RegVisit	Randomisation 1	CervicalCentile		Chris Braithwaite		Value is unobtainable.
5	2015/09/03 11:55:15	Raised	RECAP/Ictu/ (1)	RegVisit	Randomisation 1	CervicalCentile		Chris Braithwaite		Please complete this question.
5	2015/09/03 11:58:56	Responded	RECAP/Ictu/ (1)	RegVisit	Randomisation 1	CervicalCentile		Chris Braithwaite		Value is unobtainable.

For site staff to add a comment to the DCR, the flag should be clicked to view the query followed by clicking 'Respond to DCR'. Text can be added to explain or raise any questions for the TC/DM's attention. This will change the flag from red to blue.

- Flag is now blue to indicate that site responded to the DCR.



- The TC/DM can then log on to MACRO and by clicking the blue flag can either close the query or add further information to the comments.

ALTERNATIVELY

- Data queries will be sent to site as DCF reports attached to an explanatory e-mail (manual or automated). The data queries should be resolved within 14 days of receipt by site staff wherever possible.

- Once data queries have been resolved at site, they must be signed by someone with authority to do so as per the site delegation log, and returned to the LCTU by post, fax, or e-mail (as a scanned pdf).

- A copy of the resolved DCF should be attached to the appropriate patient record.

LCTU

All resolved data clarification forms (DCFs) that are sent to the LCTU should be date stamped and processed thus:

- Data should be changed in MACRO according to the information contained on the DCF and data queries resolved on the database. The DCF should be filed with the relevant CRF pages within the patient's folder.

- There is a 14 day timeframe for sites to respond to the data queries. After the 14 day deadline the DEFeND trial team will contact the site via phone or an additional email to check the status of the data query.

- All data queries are considered a potential training issue, the importance of which is dependent on the severity and frequency that a particular query is

raised. This will be monitored by the trial management team, and the number of data queries per site will be regularly reviewed by trial management (see Trial Monitoring Plan SSDEF_D010). Any training requirements identified from this process will be added to the Site Status database and reviewed by the trial co-ordinator.

4. Other Related Standard Operating Procedures (SOPs) and Documents

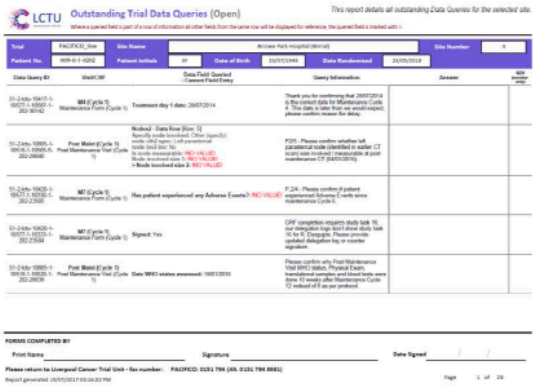
DM003	SOP for Designing a Data Query Process Plan
DM005	SOP for Designing a Data Management Plan
IS006	MACRO Database Design and Validation
TM012	Case Report Form Completion

5. Acronyms and Definitions

CRF	Case Report Form
DCF	Data Clarification Form
DCR	Data Clarification Request
DM	Data Manager
DQ	Data Query
LCTU	Liverpool Cancer Trials Unit
TC	Trial Coordinator

6. APPENDIX

6.1 Appendix 1: Example of Data Clarification Form (DCF)



LCTU **Outstanding Trial Data Queries (Open)**

This report details all outstanding Data Queries for the selected site.

Trial	PACIFICO_live	Site Name	Arrows Park Hospital (99010)	Site Number	9
Patient No.	009-9-1-0202	Patient Initials	SF	Date of Birth: 22/07/1946	Date Randomised 23/05/2013

Data Query ID	Visit/CRF	Data Field Queried / Current Field Entry	Query Information	Answer	N/A (only if asked)
51-24dv-19417-1-19577-1-19587-1-282-36142	M4 (Cycle 1) Maintenance Form (Cycle 1)	Treatment day 1 date: 26/07/2014	Thank you for confirming that 26/07/2014 is the correct date for Maintenance Cycle 4. This date is later than we would expect, please confirm reason for delay.		
51-24dv-19905-1-19938-1-19905-5-282-28040	Post Maint (Cycle 1) Post Maintenance Visit (Cycle 1)	Nodes2 - Data Row [Row: 1] Specify node involved: Other (specify): node chd type: Left paratracheal node chd size: 1.2 Is node measurable: INCORRECT VALUE Node involved size 1: INCORRECT VALUE > Node involved size 2: INCORRECT VALUE	F23 - Please confirm whether left paratracheal node (identified in earlier CT scan) was involved / measurable at post maintenance CT (04/01/2016).		
51-24dv-19426-1-19577-1-19733-1-282-23585	M7 (Cycle 1) Maintenance Form (Cycle 1)	Has patient experienced any Adverse Events?: INCORRECT VALUE	F-24 - Please confirm if patient experienced Adverse Events terms maintenance Cycle 6.		
51-24dv-19426-1-19577-1-19733-1-282-23584	M7 (Cycle 1) Maintenance Form (Cycle 1)	Signed: Yes	CRF completion requires study task 16 our delegation logs don't show study task 16 for K. Dasgupta. Please provide updated delegation log or counter signature.		
51-24dv-19905-1-19938-1-19938-1-282-28038	Post Maint (Cycle 1) Post Maintenance Visit (Cycle 1)	Date WHO states assessed: 15/01/2015	Please confirm why Post Maintenance Visit WHO status, Physical Exam, Hematology and Biochemistry tests were done 10 weeks after Maintenance Cycle 12 instead of 8 as per protocol.		

FORMS COMPLETED BY

Print Name _____ Signature _____ Date Signed ____/____/____

Please return to Liverpool Cancer Trial Unit - fax number: PACIFICO: 0151 794 (AN: 0151 794 8981)

Report generated: 26/07/2017 03:24:22 PM Page 1 of 28

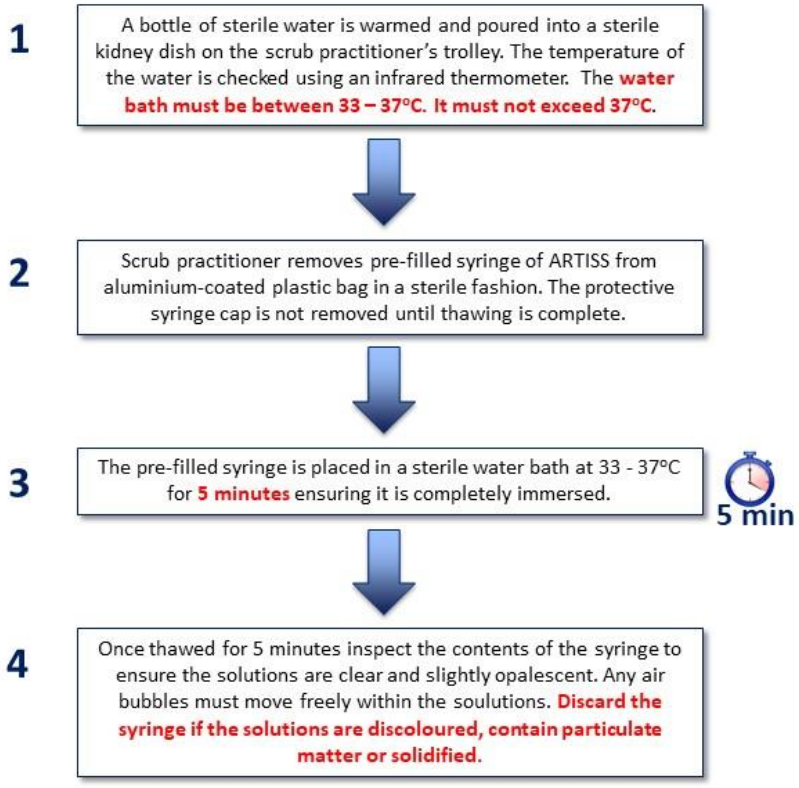
Appendix C. Preparation and Administration Protocols

C.1 Quick Thaw Protocol

DEFeND

Preparation using "Quick Thaw" technique in a sterile water bath

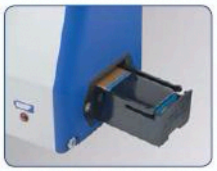
Please remember that any **clinicians who will be assessing study outcomes for the patient must leave theatre prior to randomisation** and not return until the theatre has been cleared of any evidence of ARTISS usage. Thank you.



C.2 EASYSPRAY Quick Reference Guide

EASYSPRAY Quick Reference Guide

Instructions for Circulating Nurse | EasySpray Pressure Regulator

1. 
Insert 9V battery into the EASYSPRAY pressure regulator device.

2. 
Connect EASYSPRAY device to IV pole or cart rail using the clamps on the back of the device.

3. 
Use suitable connection tube to connect the EASYSPRAY device to medical air (ranging 3.5 – 7 bar / 50 – 100 psi).

4. 
Connect Spray Set filters to EASYSPRAY device. Connect the blue filter to the blue female luer connector and the clear filter to the male luer connector.

5. 
Turn the on/off switch on the front side of the EASYSPRAY to the ON position.

6. 
Check the gauge on the EASYSPRAY device for the appropriate pressure range of 1.5-2.0 bars (21.5-28.5 psi). Adjust pressure setting by turning the black pressure control knob.

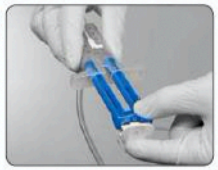
Instructions for Scrub Nurse | Spray Set

1. 
Prepare ARTISS Solution for Sealants according to the instructions in the package insert.

2. 
Firmly attach the spray head to the nozzle of the syringes.

3. 
Fasten the pull strap to the double syringe system to assure the spray head is tightly secured.

4. 
Fit the connection tube of the spray set to the luer-lock connector on the underside of the spray head.

5. 
Attach the clip (on the end of the sensor line) by sliding it into the grooves located on the top of the syringe plunger.

6. 
Pass the assembled applicator to the surgeon for spray application. Pass the end of the connection tube with the sterile filters to the circulating nurse.

Instructions for Surgeon

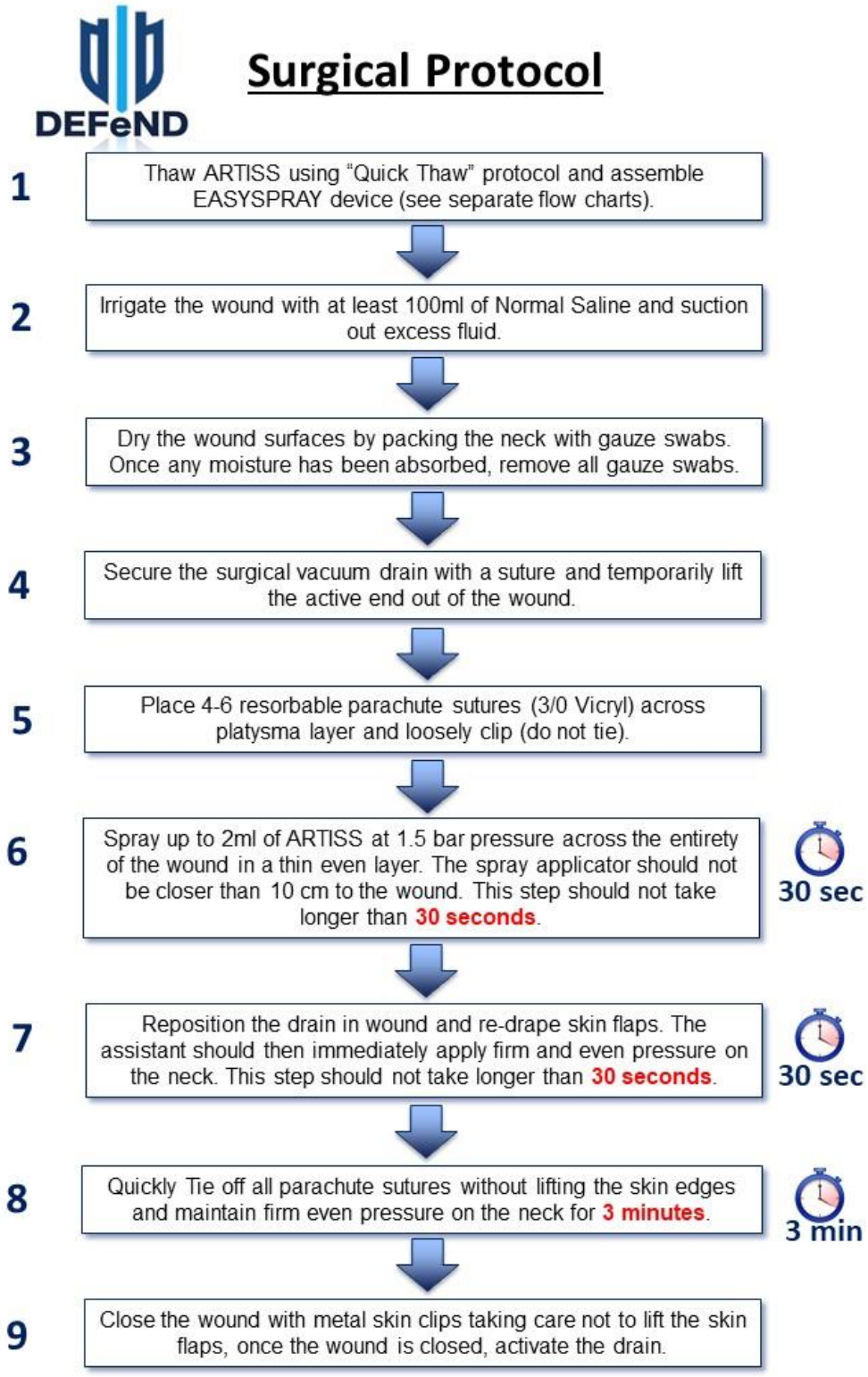
1. 
Spray from a distance of 10 – 15 cm for optimum results.

2. 
To activate the flow of gas occlude the opening in the clip center with thumb. To begin application, gently depress the syringe plunger.

The EASYSPRAY device will continue to emit gas for a brief period after the thumb is removed from the clip/plunger. This delay helps to avoid clogging of the spray head.

Please see the ARTISS abbreviated summary of product characteristics (SPC) on the back.

C.3 Surgical Protocol



Appendix D. Clavien-Dindo Classification of Surgical Complications Adapted to Common Head & Neck Complications

Post-operative Complication	Description of Severity	Clavien-Dindo Grade
Neck Wound Infection	Localised and superficial to platysma e.g. stitch abscess	**I**
	Spreading cellulitis or superficial wound infection with no underlying collection treated with antibiotics	**II**
	Collection deep to platysma requiring drainage (not under GA)	**IIIa**
	Collection deep to platysma requiring drainage (under GA)	**IIIb**
	Large collection with organ and/or life threatening sequelae (i.e. airway obstruction, severe sepsis, septic shock)	**IV** (**a** or **b** depending on organ dysfunction)

Other Surgical Site Infection	Localised infection requiring topical or non-invasive treatment	**I**
	Infection requiring treatment with antibiotics only	**II**
	Collection requiring drainage (not under GA)	**IIIa**
	Collection requiring drainage (under GA)	**IIIb**
	Large collection with organ and/or life threatening sequelae (i.e. airway obstruction, severe sepsis, septic shock)	**IV** (**a** or **b** depending on organ dysfunction
Bleeding/Haematoma	Haematoma not requiring drainage or suitable for simple aspiration with a needle (not radiologically guided)	**I**
	Need for blood transfusion	**II**
	Requiring drainage (not under GA). Includes	**IIIa**

	radiologically guided aspiration/drainage	
	Requiring drainage or return to theatre for haemostasis (under GA)	**IIIb**
	Haematoma/haemorrhage sufficiently large to obstruct airway or cause hypovolaemic shock	**IV** (**a** or **b** depending on organ dysfunction)
Chyle Leak	Low output leak (<500ml/24hrs) suitable for low fat diet and compression only	**I**
	Requirement for pharmacological management including Total Parenteral Nutrition	**II**
	Radiologically guided occlusion	**IIIa**
	Return to theatre for procedure under GA	**IIIb**
	Evidence of end organ dysfunction	**IV**

		(**a** or **b** depending on organ dysfunction)
Wound Breakdown	Superficial skin dehiscence (platysma layer intact) managed with dressings	**I**
	Small fistula managed by an enteral tube or parenteral nutrition only	**II**
	Deep dehiscence (through platysma layer) or fistula managed with procedure not under GA	**IIIa**
	Deep dehiscence (through platysma layer) or fistula managed with procedure under GA	**IIIb**
	Evidence of end organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Seroma/sialocele	Small collection not requiring drainage or suitable for aspiration with a needle (not radiologically guided)	**I**

	Salivary fistula managed medically (e.g. anticholinergic)	**II**
	Requiring drainage (not under GA). Includes radiologically guided aspiration/drainage	**IIIa**
	Requiring re-exploration and/or drainage (under GA)	**IIIb**
	Large collection obstructing airway	**IVa**
Hypersensitivity	Mild reaction not requiring treatment	**I**
	Mild/moderate/severe reaction treated with medication (e.g. antihistamine and/or steroid and/or adrenaline)	**II**
	Anaphylactic shock	**IV** (**a** or **b** depending on organ dysfunction)

Air embolism	By definition clinically evident air embolism results in cardiorespiratory dysfunction	**IVb**
Pneumothorax/Haemothorax	Small pneumothorax managed without a chest drain	**I**
	Pneumothorax/Haemothorax without respiratory failure requiring chest drain	**IIIa**
	Evidence of respiratory failure or any other organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Pulmonary Embolism	Small PE without evidence of respiratory failure managed with anticoagulation only	**II**
	Evidence of respiratory failure or any other organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Deep Vein Thrombosis	Managed with anticoagulation only	**II**

	Need for endovascular intervention including filters not under GA	**IIIa**
	Need for endovascular intervention or surgical thrombectomy under GA	**IIIb**
Lower Respiratory Tract Infection (including aspiration)	Managed with physiotherapy only	**I**
	Managed with antibiotics	**II**
	Evidence of respiratory failure or any other organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)

GA General Anaesthesia.

Appendix E. CORRECTIVE & PREVENTIVE ACTIONS (CAPA)

E.1 CAPA number 1

Liverpool Cancer Trials Unit

Corrective Action and Preventive Action Form

CAPA No: 1

Trial Title and EudraCT Number(if applicable): DEFeND

Category: LCTU Protocol Deviation ☒ Nonconformity ☐ Suggestion for improvement ☐ Safety Reporting Timelines ☐ Training issue ☒

Audit Finding ☐ Incorrect document control ☐ System failure ☒ Sponsor reported anomaly ☐ SOP deviation ☐ Other ☐ Please Specify: _____

Raised by: Mandeep Bajwa	**Person with overall responsibility for completion:** Mandeep Bajwa	**Date Raised: 20/11/2018**

How was the issue identified: Through incomplete data entry and Database checks

Description of issue:
1) Reveal of allocation occurred 3 hours prior to protocol
2) CRF not completed in operating theatre resulting in missing data fields
3) Surgeon completing operation note broke the blind by entering the fact that the patient received the intervention

Impact on:
(a) Sponsor: Minor ☐ Major ☒ Critical ☐ (please tick appropriate)
(b) Trials Unit: Minor ☐ Major ☒ Critical ☐ (please tick appropriate)
(c) Trial: Minor ☐ Major ☒ Critical ☐ (please tick appropriate)

Proposed immediate (corrective) action(s) (please list all below and add extra rows if required):

No	Description of action	Person allocated	Estimated date for completion	Date completed
1)	**Additional education for surgical team(s) in pre op setting and also through greater presence of research staff in operating theatre.** **Improved oversight of perioperative management to ensure protocol is adhered to**	**Aintree Research Nurses,** **PI; Bajwa**	**01/12/2018**	**01/12/2018**
2)	**Recruiting surgeons (consultants) and their surgical teams to take**	**Aintree Research Nurses,**	**21/11/2018**	**21/11/2018**

	more responsibility to ensure trial patients are recognised, protocols are adhered to and CRFs completed. **Site PI and research staff to re-iterate the importance of protocol adherence.**	**PI; Bajwa**		
3)				
4)				
Remarks:				

Root cause analysis required: **Yes** ☐ **No** ☒		
Underlying / root cause: Theatre staff and surgical teams unfamiliar with protocol		
Determined by: Mandeep Bajwa	**Date:** 21/11/2018	**Remarks:**

Proposed action for long term preventive actions (please list all below and add extra rows if required):

No	Description of action	Person allocated	Estimated date for completion	Date completed
1)	**Increased presence of research team and PI for site in perioperative setting should ensure protocol adherence**	**Aintree Research Nurses,** **PI; Bajwa**		
2)	**eCRF assessment as per pervious (daily) to ensure adequate and sustained data entry**	**PI; Bajwa**		
3)	**This will be discussed in next TMG meeting**	**CI; Schache** **PI; Bajwa**		
4)				
Remarks:				

To be completed by LCTU Senior Management Team/ Pharmacovigilance Committee	**Date of Meeting:**
Evidence of Completion (please list):	

Liverpool Cancer Trials Unit

Corrective Action and Preventive Action Form

CAPA No: 2

Trial Title and EudraCT Number(if applicable): DEFeND

Category: LCTU Protocol Deviation ☐ Nonconformity ☐ Suggestion for improvement ☐ Safety Reporting Timelines ☐ Training issue ☐

Audit Finding ☐ Incorrect document control ☐ System failure ☒ Sponsor reported anomaly ☐ SOP deviation ☐ Other ☐ Please Specify: _____

Raised by: Mandeep Bajwa	**Person with overall responsibility for completion:** Mandeep Bajwa	**Date Raised: 23/01/2018**

How was the issue identified: Inability to reveal patient's allocation in a timely fashion

Description of issue:
1) IT staff member off sick and unable to add consultant surgeon to MACRO/TARDIS to reveal allocation
2) Unable to get through to other members of IT department via telephone to add consultant to MACRO/TARDIS
3) Decided to use another consultant surgeon, who already had MACRO/TARDIS login to reveal the allocation and relay this information to operating team
4) Second consultant's password did not work!
5) The reveal for DEFeND patients is time sensitive and the allocation could not be revealed in this case – patient's operation was prolonged due to this system failure
6) To avoid any further time wastage the default position in these circumstances is to empirically assign patient to the control arm

Impact on:
(a) Sponsor: Minor ☒ Major ☐ Critical ☐ (please tick appropriate)
(b) Trials Unit: Minor ☒ Major ☐ Critical ☐ (please tick appropriate)
(c) Trial: Minor ☐ Major ☒ Critical ☐ (please tick appropriate)

Proposed immediate (corrective) action(s) (please list all below and add extra rows if required):

No	Description of action	Person allocated	Estimated date for completion	Date completed
1)	**CI and TC are now copied in to the email that reveals allocation. If this situation were to recur then the CI can be contacted to reveal the allocation. If the CI cannot reveal the allocation the TC will be the next port of call.**	**CI; Schache** **PI; Bajwa**	**07/12/2018**	**07/12/2018**

2)	**The issue around IT not picking up their phones to support a colleague who is off sick should be addressed by senior trial staff**	**Senior LCTU staff**	**n/a**	**n/a**
3)				
4)				
Remarks:				

Root cause analysis required: **Yes** ☐ **No** ☒

Underlying / root cause: IT system failure

Determined by: Mandeep Bajwa	**Date:** 07/12/2018	**Remarks:**

Proposed action for long term preventive actions (please list all below and add extra rows if required):

No	Description of action	Person allocated	Estimated date for completion	Date completed
1)	**CI and TC are now copied in to the email that reveals allocation. If this situation were to recur then the CI can be contacted to reveal the allocation. If the CI cannot reveal the allocation the TC will be the next port of call.**	**CI; Schache** **PI; Bajwa**	**07/12/2018**	**07/12/2018**
2)				
3)				
4)				
Remarks:				

To be completed by LCTU Senior Management Team/ Pharmacovigilance Committee	**Date of Meeting:**
Evidence of Completion (please list):	
Comments on effectiveness of long term action/prevention taken:	